


IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

WYETH LLC, WYETH	)	
PHARMACEUTICALS LLC, PF PRISM	)	
C.V., PFIZER PHARMACEUTICALS LLC,	)	Redacted- Public Version
and PFIZER PFE IRELAND	)	
PHARMACEUTICALS HOLDING 1 B.V.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 16-1305-RGA
	)	
ALEMBIC PHARMACEUTICALS, LTD., <i>et</i>	)	<b>CONSOLIDATED</b>
<i>al.</i>	)	
	)	
Defendants.	)	

**BRIEF IN SUPPORT OF SUN'S MOTION TO EXCLUDE  
THE OPINIONS AND TESTIMONY OF BERNHARDT TROUT, PH.D**

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## **I. Nature and Stage of the Proceedings**

This is a patent infringement action relating to the alleged infringement and invalidity of three patents which purportedly cover Plaintiffs' marketed product containing bosutinib. The parties have completed expert discovery, including expert reports and expert deposition and are preparing for trial in early November. In the Scheduling Order the Court allowed Daubert briefing at the end of expert discovery, and Sun presents this brief in support of its Motion to Exclude the Testimony and Opinions of Bernhardt Trout, Ph.D.

## **II. Summary of Argument and Statement of Facts**

Dr. Trout was engaged by Plaintiffs as one of four (4) individuals to respond to the Opening Invalidity Report of Dr. Craig Lindsley. Specifically, Dr. Trout was asked to respond to Dr. Lindsley's opinion that U.S. Patent No. 7,919,625 ("the '625 patent") is invalid due to anticipation.<sup>1</sup> Dr. Trout opines "a POSA reading Boschelli 2001 would not have understood it to disclose a pharmaceutical composition comprising bosutinib. Thus, my opinion is that Boschelli 2001 does not anticipate the '625 patent." Ex. A (Trout Rpt). ¶ 81. Sun seeks to exclude the opinions and testimony of Dr. Trout because he does not have the requisite knowledge, expertise or understanding of the pertinent art to opine on anticipation of the '625 patent and his opinions are not reliable. More specifically and explained in more detail below:

1. Dr. Trout does not qualify as a Person of Ordinary Skill in the Art ("POSA")
2. Dr. Trout does not understand the process or requirements for animal studies in drug development
3. Dr. Trout is unable to define "pharmaceutically acceptable composition"

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<sup>1</sup> Dr. Lindsley offers additional opinions regarding invalidity due to obviousness, lack of written description, enablement and indefiniteness, which are responded to by three other individuals retained by Plaintiffs.

4. Dr. Trout walks away from and contradicts the opinions expressed in his report
5. Dr. Trout “does not have an opinion” on fundamental issues relating to his opinion and conclusions.

### **III. Legal Standards**

The Federal Rules of Evidence “assign to the trial judge the task of ensuring that an expert’s testimony both rests on a reliable foundation and is relevant to the task at hand.” *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). “Rule 702 has three requirements: (1) the proffered witness must be an expert, *i.e.*, must be qualified; (2) the expert must testify about matters requiring specific, technical or specialized knowledge, *i.e.*, must be reliable; and (3) the expert’s testimony must assist the trier of fact, *i.e.*, must be fit.” *Meadows v. Anchor Longwall and Rebuild, Inc.*, 306 Fed. App’x. 781, 788 (3d Cir. 2009). The relevant factors to be considered when assessing the reliability of an expert’s testimony include: “(1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique’s operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.” *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir. 2000) (citing *In re Paoli*, 35 F.3d at 742 n.8). However, the list is “nonexclusive” and “each factor need not be applied in every case.” *Elcock v. Kmart Corp.*, 233 F.3d 734, 741 (3d Cir. 2000). The party offering the expert testimony has the burden of establishing its admissibility by a preponderance of the evidence. *Bourjaily v. United States*, 483 U.S. 171, 175–76 (1987).

The qualification requirement examines whether the witness has “specialized knowledge or training sufficient to qualify him to opine on an issue within his field of expertise.” *Pell v. E.I. DuPont De Nemours & Co.*, 231 F.R.D. 186, 192 (D. Del. 2005). In a patent case, an expert testifying on validity or infringement must have at least the expertise of a person of ordinary skill in the art (“POSA”). *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008). Further, an expert’s opinions “must be confined to [the expert’s] field” of expertise. *Pell*, 231 F.R.D. at 192. “An expert may be generally qualified but may lack qualifications to testify outside his area of expertise.” *Calhoun*, 350 F.3d 322 (holding that expert in investigating “aquatic related accident[s]” could testify about “different types of jet skis and their operation,” but not whether specific jet ski designs were safe). The more specific the opinions given, the more specific the knowledge required. *Calhoun*, 350 F.3d at 322. Rule 702 “clearly contemplates some degree of regulation of the subjects and theories about which an expert may testify.” *Daubert*, 509 U.S. at 589.

#### **IV. Dr. Trout’s Opinions and Testimony Regarding Anticipation of the ‘625 Patent Should be Excluded**

##### **A. Dr. Trout is Not Qualified to Opine Regarding Anticipation of the ‘625 Patent**

##### **1. Dr. Trout Does Not Qualify as a Person of Ordinary Skill in the Art**

At the outset, Dr. Trout does not qualify as a POSA under either party’s definition and most certainly does not qualify as a POSA under Pfizer’s definition. In his report, Dr. Trout notes Pfizer’s definition of a POSA is:

someone having the knowledge of (1) an M.D. with several years of experience as an oncologist treating patients with CML; (2) a Ph.D. with several years of experience conducting research on inhibition of tyrosine kinases; and (3) a person with a Ph.D in medicinal chemistry, pharmacology or a related field with several

years of experience in drug development and formulation. *See* Ex. B (Trout Rpt) ¶25, citing D.I. 91 at 4.

Dr. Trout goes on to note under Pfizer's proposal, a **single** hypothetical individual would have all of the relevant experience. Ex A. (Trout Rpt.) ¶ 27. At his deposition, Dr. Trout admitted he is not POSA under Pfizer's full definition and qualifies his "skill is really focused on the third part of that definition." Ex. B (Trout Tr.) at 21:7-14. Under Sun's definition Dr. Trout similarly fails to meet the standard for a POSA. Sun's proposed definition is a person with:

a high level of skill, such as an M.D. and several years of experience as an oncologist treating patients with CML, or a Ph.D. and several years of experience conducting research on inhibition of tyrosine kinases. A POSA would have access to and could have collated with individual with pertinent experience, such as medicinal chemistry, biology, pharmacology and/or drug metabolism and pharmacokinetics. A POSA could have a lower degree of formal education is such person had a high degree of expertise. D.I. 91 at 5.

Dr. Trout does not have any experience with the treatment for CML, "outside of just reading the documents in this case." Ex. B. (Trout Tr.) at 12:21-24. Prior to his engagement in this matter, Dr. Trout did not have a specific or detailed understanding of CML, other than knowing Gleevec was a pharmaceutical for the treatment of cancer. *Id.* at 12:25-13:12. Dr. Trout gained his understanding of CML ("to the extent [he has] an understanding") from the '625 patent, the background in Dr. Lindsley's report and some of the exhibits. *Id.* at 14:5-15. Dr. Trout admitted he does not have any experience conducting research specifically on inhibition of tyrosine kinases. *Id.* 15:12-18. Further, his background knowledge on inhibition of tyrosine kinases is general in terms of his study of drug development and inhibition broadly, his understanding is not specific as it relates to the treatment of CML, and his understanding of the role of inhibition of tyrosine kinases in the treatment for CML is based on his general educational background and the documents he reviewed for this matter. *Id.* at 15:19-16:19.

Prior to his engagement in this matter, he did not have any specific understanding of how tyrosine kinases and/or their inhibition were implicated in CML therapy. *Id.* at 16:20-16:25.

In a patent case, an expert testifying on validity or infringement must have at least the expertise of a person of ordinary skill in the art (“POSA”). *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008) In this case, the issues call for consideration of evidence from the perspective of a POSA, and it would be “contradictory to Rule 702 to allow a witness to testify on the issue who is not qualified as a technical expert in that art.” *Id.* More specifically, “a witness not qualified in the pertinent art may not testify as an expert as to anticipation, or any of the underlying questions, such as the nature of the claimed invention, what a prior art references discloses, or whether the asserted claims read on the prior art reference.” *Id.* at 1364. Based on Dr. Trout’s background and his testimony, his knowledge and experience do not qualify him as a POSA nor is his expertise appropriately relevant to the pertinent art. Dr. Trout’s testimony should be excluded as he is not qualified to opine in relation to the pertinent art and his testimony will not assist the trier of fact.

## **2. Dr. Trout Fundamentally Does Not Understand the Process or Requirements for Animal Studies in Drug Development**

Dr. Trout correctly notes an anticipation defense focuses on “whether a POSA would *reasonably understand or infer* that every claim element is disclosed in that reference.” Ex. A (Trout Rpt.) ¶31 (emphasis added). However, Dr. Trout’s testimony and misunderstanding of the pertinent art makes it clear he is unable to testify as to what a POSA would reasonably understand or infer Boschelli 2001 to disclose. Dr. Trout repeatedly makes incorrect and contradictory assumptions and conclusions, and fails to provide knowledge or opinions relating to the pertinent art.



Dr. Trout criticizes the Boschelli 2001 reference and determines it does not anticipate the '625 patent, because it was not clear to him "the researches took care to synthesize [bosutinib] for use in animal studies such that the active compound being evaluated would be "pharmaceutically acceptable." Ex. A (Trout Rpt) ¶ 68. He further criticizes Boschelli for not disclosing "that the research took care to procure and use pharmaceutical grade excipients when preparing the composition administered in the reported animal studies." Ex. A (Trout Rpt) ¶ 74. The basis for his opinion is premised on a misreading of the prior art.

A principal reference Dr. Trout relies on for this opinion is Wolff 2003. When specifically confronted with the Wolff reference Dr. Trout admitted Wolff states the use of non-pharmaceutical grade excipients should be based on 1) scientific necessity 2) nonavailability of an acceptable veterinary or human pharmaceutical grade compound and 3) specific review and approval by the IACUC. Ex. B. (Trout Tr.) at 79:14-21. In line with the disclosure of Wolff, Dr. Trout was asked what in Boschelli would lead him to believe there was a scientific necessity to use non-pharmaceutical grade excipients. His response was "I would say it the other way around. There was not a scientific necessity for Boschelli to use pharmaceutical grade compounds." Ex. B. (Trout Tr.) at 79:23-80:7. This is directly contradictory to Wolff, the very reference Dr. Trout relies upon to justify his opinions. Dr. Trout's misinterpretation of Wolff highlights his lack of understanding of the basics relating to animal research.

Dr. Trout's misunderstanding is understandable given he has never conducted animal research. Further, he admitted he did not consult with any of his colleagues who conduct animal research to determine their standard practice. Ex. B. (Trout Tr.) at 81:18-23. Dr. Trout could not state whether a POSA in the art reading Boschelli would believe it was more likely than not that the TWEEN 80 used in Boschelli was pharmaceutical grade, only that there was no indication it

was pharmaceutical grade. Ex. B. (Trout Tr.) at 92:11-93:2. However, based on Wolff and other references, it is clear a POSA would reasonably understand or infer pharmaceutical grade excipients were used, because that is the standard and there was no indication otherwise. *See* Ex. C (Wolff).

Dr. Trout concedes a pharmaceutical composition according to the '625 patent includes compositions formulated for use in animal laboratory research. The Boschelli reference is directed to use of a composition in just such a context. However, Dr. Trout has never done research in laboratory animals and has never read the two governing documents setting out the standards for laboratory research in animals. Ex. B. (Trout Tr.) at 36:25-38:21. Not surprisingly, when confronted with questions regarding the requirements relating to animal research, Dr. Trout repeatedly responded with "I don't have an opinion on that." *See* Ex. B (Trout Tr. 106:18-108:18). Specifically, Dr. Trout was asked whether researchers working with laboratory animals have a duty to ensure the research causes the least possible harm to the animal - Dr. Trout did not have an opinion. Dr. Trout did also did not have an understanding as to the requirements for providing veterinary care to laboratory animals. and did not have an opinion

A POSA reading the Boschelli reference *would* have an understanding of the requirements for conducting laboratory research and it would have informed their understanding and inference of what the Boschelli reference discloses. Dr. Trout is unable to, and indeed does not, provide any reliable opinions on what a POSA would reasonably understand or infer Boschelli to be disclosing about the composition used in the animal studies. As such, Dr. Trout lacks the necessary knowledge and understanding of the pertinent art to testify in this matter and his testimony should be excluded.

**B. Dr. Trout Is Unable to Define "Pharmaceutically Acceptable Composition"**

The opinion Dr. Trout purports to offer is exceedingly narrow, namely that the Boschelli reference *does not* say the composition it uses to inhibit tumors in mice is a “pharmaceutically acceptable” composition. In fact, Dr. Trout never offers the opinion the composition of Boschelli is *not* pharmaceutically acceptable. *See e.g.* Ex. B (Trout Tr.) at 151:24-152:11. It is not surprising he is unable to reach that conclusion given Dr. Trout was unable to define the criteria one would have to meet to arrive at a “pharmaceutically acceptable” composition.

Dr. Trout offered the opinion Boschelli does not disclose a “pharmaceutically acceptable” composition because (1) the bosutinib was *likely* not pure; and (2) Boschelli does not disclose the excipients used were pharmaceutical grade excipients. Ex. A (Trout Rpt.) ¶¶66-74.<sup>2</sup> However, when asked if the composition of Boschelli would be “pharmaceutically acceptable” if it used pure bosutinib and pharmaceutical grade excipients, Dr. Trout didn’t have an opinion. Ex. B (Trout Tr.) at 72:6-75:24. He also didn’t form an opinion as to whether the composition could have been reproduced in such a way to make it pharmaceutically acceptable. *Id.* at 157:17-158:3.

Dr. Trout’s failure underpins the fact he cannot say what a “pharmaceutically acceptable” composition would be in the context of the ‘625 patent. Dr. Trout was repeatedly asked what, if anything, would be pharmaceutically acceptable pursuant to the claims. He was unable to do so. *See* Ex. B (Trout Tr.) at 133:4-138:6; 141:11-23; 149:8-150:9. In fact, Dr. Trout does not even know if the *only composition* disclosed in the ‘625 patent is a pharmaceutically acceptable composition. Ex. B (Trout Tr.) at 165:19-166:7. Dr. Trout’s opinions are fundamentally unreliable because he cannot say with any degree of clarity of thought what would constitute a pharmaceutically acceptable composition as that term is used in the ‘625 patent.

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<sup>2</sup> Dr. Trout agrees every excipient used in the Boschelli composition are disclosed in the ‘625 patent and are generally recognized as safe by FDA.

**C. Dr. Trout Repeatedly Walks Away From or Contradicts the Opinions Expressed in His Expert Report**

Throughout Dr. Trout's deposition, he contradicted his own expert report by stating he had no opinion on things he explicitly addressed in his report.

In Dr. Trout's report he offers the opinion "the mice [in the Boscelli experiment] did not have CML, and [bosutinib] was not being administered to provide a therapeutic benefit." Ex. A (Trout Rpt) ¶ 67. Dr. Trout's opinions are further premised on his belief the API used in the experiments were being produced for "screening experiments." *See, e.g., id* at ¶ 69. But at his deposition, Dr. Trout was asked what the objective was of administering the composition to the mice and he answered he didn't have an opinion:

Q: What was the objective of the Boschelli folks in administering the composition containing bosutinib, Tween 80 and dextrose?"

...

A: I didn't speak in my report about the specific objective, so I didn't express an opinion about that."

Ex. B (Trout Tr.) at 145:22-146:5; *see also* 146:19-147:15.

It is fundamentally contradictory to on the one hand express an opinion about the reason a composition was being administered to the mice and simultaneously testify he did not consider why the compositions were being administered to the said same mice. Put differently, Dr. Trout cannot simultaneously offer opinions a composition was "not being administered to provide a therapeutic benefit" and the API was being produced to be used in "screening experiments" and testify he has no opinion about the objective of administering the composition to laboratory animals.

Dr. Trout's failure to offer an opinion on why the composition was being administered further undercuts his related testimony that one would have to have an understanding of the

objectives of administering a compound to understand whether it was a “pharmaceutically acceptable composition.”

Q: Do you have an opinion about what a composition administered to a laboratory animal would have to look like in order for it to be considered pharmaceutically acceptable?

A: ... And, again, it would depend on the context, what the study was done for, and I would have to analyze those details.”

Ex. B. (Trout Tr.) at 141:11-23.

As previously demonstrated, Dr. Trout cannot define what a “pharmaceutically acceptable composition” is, does not know whether the composition of Boschelli is “pharmaceutically acceptable” and is not qualified to ascertain whether a POSA would reasonably understand or infer it was pharmaceutically acceptable. Furthermore, Dr. Trout failed to undertake the very same analysis he testified was necessary to determine whether the composition was pharmaceutically acceptable. In view of this failure alone, he should not be permitted to testify as to the anticipation of the sole asserted claim of the ‘625 patent.

**D. Dr. Trout “Does not Have an Opinion” on Fundamental Issues Relating to His Opinion**

Dr. Trout was either unable or unwilling to offer multiple opinions central to his ultimate conclusions. For example, Dr. Trout testified he does not have an opinion/understanding as to whether or not Claim 1 of the ‘625 patent requires treating CML with a pharmaceutically acceptable composition. Ex. B (Trout Tr.) at 48:25-49:8. Further, as noted above, in reviewing the ‘625 patent, Dr. Trout made clear he did not have an opinion as to whether the composition disclosed in the patent described a pharmaceutically acceptable composition. Ex. B (Trout Tr.) at 165:19-166:2.

Further, should Dr. Trout be allowed to testify at trial, Dr. Trout should not be allowed to offer any testimony or opinion regarding any alleged interchangeability of the terms “treating”

and “inhibiting” as used in the ‘625 patent. Ex. A (Trout Rpt.) ¶37, fn. 1. At Dr. Trout’s deposition he stated he did not use those terms interchangeably in formulating his opinions, but was “observing that I think the ‘625 patent does so.” Ex. B (Trout Tr.) at 22:17-23:11. This statement is consistent with his repeated testimony that he does not understand or did not analyze issues central to his opinions and this matter.

## **V. Conclusion**

Based on the foregoing, Sun respectfully requests this Court entering an Order excluding Dr. Trout’s opinions and testimony from being presented or relied upon in this matter.

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# **Exhibit A**

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

WYETH LLC, WYETH )  
PHARMACEUTICALS LLC, PF PRISM C.V., )  
PFIZER PHARMACEUTICALS LLC, and )  
PFIZER PFE IRELAND )  
PHARMACEUTICALS HOLDING 1 B.V., )

Plaintiffs,

v.

ALEMBIC PHARMACEUTICALS, LTD., )  
ALEMBIC PHARMACEUTICALS, INC., SUN )  
PHARMACEUTICAL INDUSTRIES )  
LIMITED, and SUN PHARMACEUTICAL )  
INDUSTRIES, INC., )

Defendants.

Redacted- Public Version

C.A. No. 1:16-cv-01305-RGA  
CONSOLIDATED



**RESPONSIVE EXPERT REPORT OF BERNHARDT L. TROUT, PH.D.  
REGARDING THE VALIDITY OF U.S. PATENT NO. 7,919,625**







[REDACTED]

[REDACTED]

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[REDACTED]

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- d. background on the '625 patent; and
- e. my opinion that claim 1 of the '625 patent is not anticipated by Boschelli 2001.

### **III. PERSON OF ORDINARY SKILL IN THE ART**

25. I understand that Pfizer has taken the position that, in the context of the '625 patent, a POSA is:

someone having the knowledge of (1) an M.D. with several years of experience as an oncologist treating patients with CML; (2) a Ph.D. with several years of experience conducting research on inhibition of tyrosine kinases; and (3) a person with a Ph.D. in medicinal chemistry, pharmacology, or a related field with several years of experience in drug development and formulation.

(Joint Claim Construction Br., D.I. 91, at 4 (Ex. D)).

26. I understand that Sun has further stated that in the context of the '625 patent:

a POSA would have a high level of skill, such as an M.D. and several years of experience as an oncologist treating patients with CML, or a Ph.D. and several years of experience conducting research on inhibition of tyrosine kinases. A POSA would have access to and could have collaborated with individuals with pertinent experience, such as a medicinal chemistry, biology, pharmacology, and/or drug metabolism and pharmacokinetics. A POSA could have a lower degree of formal education if such person had a higher degree of experience.

(Ex. D at 5).

27. It is my understanding that Pfizer and Sun do not dispute the type of experience to which a POSA would have access. In Pfizer's proposal, a single hypothetical individual would have all of the relevant experience. In Sun's proposal, the narrower experience of one individual would be supplemented by the knowledge of team members regarding other disciplines. My opinions are the same regardless of which definition is applied.

### **IV. LEGAL STANDARDS**

28. I am informed that Sun has challenged the validity of the one claim set forth in the '625 patent on several grounds including, *inter alia*, anticipation.

**A. Claim Construction**

29. I understand that the validity of the '625 patent must be evaluated in light of the claim that appears in the '625 patent as properly construed. I have read Judge Andrews' June 27, 2018 claim construction opinion, (Markman Order, D.I. 98) (Ex. E), which construed a term in the claim of the '625 patent as follows:

Claim Term	Court's Construction
"pharmaceutical composition" ( '625 patent claim 1)	"a pharmaceutically acceptable composition containing the specified compound and one or more excipients"

(Ex. E at 1).

30. I have applied this construction in performing the analysis in this report.

**B. Anticipation**

31. I have been advised by Pfizer's lawyers that for a reference to anticipate a patent claim, it must disclose every element of that claim. The question is not whether a prior art reference suggests each element, but whether a POSA would reasonably understand or infer that every claim element is disclosed in that reference.

32. I further understand that, in order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation.

**V. INFORMATION AND MATERIALS CONSIDERED**

33. In preparing this report, I have reviewed and relied upon the materials listed in Exhibit F, including the materials cited and listed in this report. My opinions are based in part on my review of those documents and materials.

34. I have also relied on my education, experience, and knowledge of industry practices as well as my understanding of the applicable legal principles described above.



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67,377, 67,378-79 (Dec. 24, 1997) (Ex. EE). The pharmaceutical composition must also be manufactured and maintained with appropriate sterility. This is particularly important for pharmaceutical compositions that are meant to be injected. (FDA Q6A Specifications, Ex. CC § 3.3.2.3(c); *see also Remington* ch. 41, Ex. AA at 783-84).

65. Finally, in a pharmaceutical composition the excipients used must be compatible with each other and with the API. (*Remington* ch. 38, Ex. K at 713-14). Such compatibility is essential in a pharmaceutical composition. Both dextrose and Tween-80 have incompatibilities with certain pharmaceuticals and other compounds that must be taken into account when developing pharmaceutical compositions that include those ingredients. (Arthur H. Kibbe, ed, *Dextrose, in Handbook of Pharmaceutical Excipients* 175, 176 (3rd ed. 2000) (Ex. FF); Arthur H. Kibbe, ed, *Polyoxyethylene Sorbitan Fatty Acid Esters, in Handbook of Pharmaceutical Excipients* 416, 419 (3rd ed. 2000) (Ex. GG)).

#### **IX. CLAIM 1 OF THE '625 PATENT IS NOT ANTICIPATED BY BOSCHELLI 2001**

66. Claim 1 of the '625 patent is not anticipated by Boschelli 2001 because Boschelli 2001 does not disclose a pharmaceutical composition comprising bosutinib.

67. As discussed above in Section VII, Boschelli 2001 discloses a newly lab-synthesized compound that is tested in animal experiments. In those animal studies reported in Boschelli 2001, human CML tumor cells were introduced into laboratory mice, and the tumors were assessed after administration of compound 31a. The mice did not have CML, and compound 31a was not being administered to provide a therapeutic benefit. The animals were to be sacrificed after testing. There is no suggestion in Boschelli 2001 that the researchers took care to develop a “pharmaceutically acceptable composition” in conducting these initial animal studies. *See Remington* ch. 10, Ex. L at 87; *Remington* ch. 39, Ex. BB at 721-22.



**A. Boschelli 2001 Does Not Disclose the Synthesis of a Pharmaceutically Acceptable API**

68. There is no disclosure in Boschelli 2001 that the researchers took care to synthesize compound 31a for use in the animal studies such that the active compound being evaluated would be “pharmaceutically acceptable.” *See Remington* ch. 10, Ex. L at 87.

69. As explained in more detail below, the chemical synthesis disclosed in Boschelli 2001 was not designed to lead to, and likely would not have led to, a pharmaceutically acceptable API. Boschelli 2001 describes an initial laboratory procedure intended to produce a material that could be used in screening experiments. (Boschelli 2001, Ex. B at 3974). Boschelli 2001 includes no indication that there was any effort to produce compound 31a under conditions suitable for its inclusion in a pharmaceutical composition or to confirm its suitability for use in a pharmaceutical composition. *See Remington* ch. 10, Ex. L at 87.

70. A POSA reading Boschelli 2001 would conclude that compound 31a was synthesized without much attention paid to purification or to any of the specifications required for active compounds that are to be included in a pharmaceutical composition; compound 31a most likely contained impurities such that it would not have been pharmaceutically acceptable.

71. As discussed above in Section VIII.A, to be pharmaceutically acceptable, an active compound must meet specifications including a maximum of net percentage impurities and maxima of each impurity. There is no indication that the main separation step disclosed in Boschelli 2001, a basic “column chromatography,” reduces impurities to pharmaceutically acceptable levels. (Boschelli 2001, Ex. B at 3974). Indeed, this separation method is not used for creating pharmaceutically acceptable actives, but rather is used only for a crude separation. When creating a pharmaceutically acceptable active, appropriate particle size and type, pressure, column length, and flow rate must all be taken into account during the separation step. Crude

column chromatography of the kind used in Boschelli 2001 does not take these factors into account. See A.M. Katti & P. Jagland, *Development and Optimization of Industrial Scale Chromatography for Use in Manufacturing*, 26 *Analisis Mag.* 38, 45-46 (1998) (Ex. HH) (discussing the conditions which must be optimized for using the chromatography process past the discovery stage). Additionally, the large range of the melting point of compound 31a reflects a large fraction of impurities in the compound. See Steven A. Hardinger, *A Simple Demonstration of the Effect of Impurities on Melting Point*, 72 *J. Chemical Educ.* 250, 250 (1995) (Ex. II).

72. Further, Boschelli 2001 does not reflect any measurement or characterization of the impurities in compound 31a or otherwise suggest that the specifications required for a pharmaceutical composition were met. See FDA Q6A Specifications, Ex. CC at §§ 3.2–3.3; see also Remington ch. 36, Ex. M at 669; Leonard C. Baily, *Ch. 33: Chromatography*, in Remington: *The Science and Practice of Pharmacy* 587, 587 (Alfonso R. Gennaro et al. eds., 20th ed. 2000) (Ex. JJ). The only characterization done of compound 31a, other than of its melting range, was aimed at confirming that compound 31a was in fact the compound the researchers had intended to synthesize. (Boschelli 2001, Ex. B at 3974).

73. Boschelli 2001's lack of attention to the impurity levels in compound 31a is also apparent in the filtration step of the synthesis. Boschelli 2001 describes the use of the solvents methanol and dichloromethane, also known as methylene chloride, in synthesizing compound 31a. (Boschelli 2001, Ex. B at 3974). The FDA categorizes both methanol and dichloromethane as Class 2 solvents and requires strict concentration limits of these solvents in pharmaceutical compositions. See FDA Q3C Impurities, Ex. EE at 67,381, Table 2. There is no indication in Boschelli 2001 that the methanol and dichloromethane left in the compound as residual solvents

were removed during the filtration step through drying. Boschelli 2001 also fails to mention any testing done to determine whether the residual solvent levels in compound 31a fell below acceptable limits.

**B. Boschelli 2001 Does Not Disclose the Use of Pharmaceutically Acceptable Excipients**

74. In addition to failing to disclose the creation of a pharmaceutically acceptable active compound, Boschelli 2001 does not disclose that the researchers took care to procure and use pharmaceutical grade excipients when preparing the composition administered in the reported animal studies. Specifically, nothing in Boschelli 2001 suggests that the inactive components of Tween-80, dextrose, and water included with compound 31a in the formulation administered to the laboratory mice were pharmaceutical grade or would have been pharmaceutically acceptable as used. *See Remington* ch. 10, Ex. L at 87; *Remington* ch. 39, Ex. BB at 721-22. As discussed above in Section VIII.B, paragraph 62, the rigorous USP-NF standards required for components of pharmaceutical compositions need not apply to the use of compounds for tests involving laboratory animals. (Wolff 2003, Ex. T at 34). Compositions used for tests involving laboratory rodents may be made with laboratory grade materials.

**C. Boschelli 2001 Does Not Disclose the Use of Procedures Required for Making Pharmaceutically Acceptable Compositions**

75. There is no indication in Boschelli 2001 that the researchers that conducted the animal testing followed production procedures that would have produced an aqueous-based pharmaceutically acceptable composition. *See Remington* ch. 41, Ex. AA at 781.

76. As discussed above in Section VIII.B, paragraph 60, the water used in pharmaceutical compositions, particularly those formulated for injection, must meet rigorous standards to ensure sterility of the composition. *See USP25-NF20 Water*, Ex. Z at 1809-10;

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# **Exhibit B**

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IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

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Civil Action No. 16-1305-RGA

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WYETH LLC, WYETH PHARMACEUTICALS INC.

5

et al.,

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Plaintiffs,

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-against-

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ALEMBIC PHARMACEUTICALS, LTD., et al.,

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Defendants.

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VIDEOTAPED DEPOSITION OF BERNHARDT TROUT, Ph.D.

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New York, New York

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Wednesday, August 7, 2019

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Reported by:

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JEFFREY BENZ, CRR, RMR

25

JOB NO. 165308

August 7, 2019  
9:04 a.m.

Videotaped Deposition of BERNHARDT TROUT, Ph.D., held at the offices of Freeborn & Peters LLP, 230 Park Avenue, New York, New York, before Jeffrey Benz, a Certified Realtime Reporter, Registered Merit Reporter and Notary Public of the State of New York.

# APPEARANCES:

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SHEPPARD, MULLIN, RICHTER & HAMPTON  
Attorneys for Defendant Alembic Pharmaceuticals, Ltd., et al.  
2099 Pennsylvania Avenue, NW  
Washington, D.C. 20006  
BY: APRIL WEISBRUCH, ESQ.

ALSO PRESENT:  
PHIL RIZZUTI, Videographer

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THE VIDEOGRAPHER: This is the start of Media labeled Number 1 of the video-recorded deposition of Bernhardt Trout in the matter of Wyeth LLC, Wyeth Pharmaceuticals Inc., et al., versus Alembic Pharmaceuticals Ltd., et al., in the United States District Court for the District of Delaware, Case Number 16-1305-RGA. This deposition is being held at 230 Park Avenue, New York, New York, on August 7, 2019, at approximately 9:04 a.m.

My name is Phil Rizzuti. I am the legal video specialist from TSG Reporting Inc. The court reporter is Jeff Benz, in association with TSG Reporting.

Counsel, please introduce yourselves.

MR. BENSON: Stephen Benson, from the firm of Freeborn & Peters, on behalf of the Sun defendants.

MS. BEIS: Kimberly Beis, also from Freeborn & Peters, on behalf of the Sun defendants.

MS. WEISBRUCH: April Weisbruch, from Sheppard, Mullin, Richter & Hampton, here

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on behalf today of Alembic.  
MS. PIPER: Stephanie Piper, from Arnold & Porter, here on behalf of the plaintiffs.

THE VIDEOGRAPHER: Will the court reporter please swear in the witness. BERNHARDT TROUT, Ph.D., called as a witness, having been first duly sworn by Jeffrey Benz, a Notary Public within and for the State of New York, was examined and testified as follows:

# EXAMINATION BY MR. BENSON:

Q. Good morning, Dr. Trout.

A. Good morning.

Q. As you heard during the introductions, my name is Stephen Benson, and I represent the Sun defendants.

And I understand from looking at your CV that this is not your first time being deposed, correct?

A. Correct.

Q. Okay. So I'm not going to go into details about the structure of a deposition,



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 2 with the understanding that you're familiar with  
 3 that. However, I will just remind you that  
 4 giving deposition testimony is equivalent to  
 5 giving testimony in a court of law, the same  
 6 requirements for truthfulness and the same  
 7 requirement that you answer completely, to the  
 8 extent that you're able, any question that is  
 9 asked. Do you understand those rules?  
 10 A. Yes.  
 11 Q. Okay. And if you don't understand a  
 12 question, please feel free to let me know. If  
 13 you want me to rephrase the question, we can do  
 14 that as well. Okay?  
 15 A. Okay.  
 16 Q. And lastly, if you need to take a  
 17 break, just let me know. I'm happy to  
 18 accommodate that. Okay?  
 19 A. Thank you.  
 20 Q. Great.  
 21 Now, you -- at some time in your  
 22 engagement in this matter you received an expert  
 23 report by a Dr. Craig Lindsley; is that correct?  
 24 A. Yes, I -- I think I received two  
 25 reports --

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 2 opinion or if it's multiple opinions. But, yes,  
 3 the focus was the anticipation of the '625.  
 4 Q. All right. Now -- were you asked to  
 5 opine on any of the other bases of invalidity  
 6 presented by Dr. Lindsley in his opening report?  
 7 A. No.  
 8 Q. Okay. Do you have any understanding  
 9 as to why you were asked specifically to address  
 10 just the anticipation argument as it relates to  
 11 the '625 patent?  
 12 A. No broader understanding. I just know  
 13 about the '625 and the opinions in my report.  
 14 Q. Okay. Having read Dr. Lindsley's  
 15 opening report, do you feel you were qualified  
 16 to address any of the other opinions  
 17 Dr. Lindsley presented as it relates to  
 18 invalidity of the '625 patent?  
 19 MS. PIPER: Objection. Outside the  
 20 scope of Dr. Trout's report and opinion.  
 21 A. My focus and my task, as I outlined in  
 22 my expert report itself, was on the '625, so I  
 23 didn't really look into the details of the  
 24 others.  
 25 Q. Okay. I think my question was just a

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 2 Q. Okay.  
 3 A. -- from Dr. Lindsley.  
 4 Q. Okay. And an opening report that  
 5 related to the invalidity of the -- let's see,  
 6 U.S. Patent Number -- let me get the full number  
 7 on the record.  
 8 7,919,625, correct?  
 9 A. Yes. I think his report discussed a  
 10 number of patents but that was the focus of my  
 11 analysis.  
 12 Q. Okay. And for the purposes of this  
 13 deposition, I'll refer to that particular patent  
 14 as "the '625 patent." Okay?  
 15 A. Okay.  
 16 Q. Now, did you read the entirety of that  
 17 opening report of Dr. Lindsley?  
 18 A. Yes.  
 19 Q. Okay. And my understanding, based on  
 20 looking at your own report, is that your  
 21 opinions are specifically focused on one opinion  
 22 provided by Dr. Lindsley relating to the  
 23 anticipation of the '625 patent; is that  
 24 correct?  
 25 A. Broadly, I'm not sure if that's one

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 2 little bit simpler. It wasn't asking you to  
 3 give an opinion. It's as to whether or not you  
 4 were able to determine, based on your review,  
 5 whether you were qualified to opine on the  
 6 issues presented in the remaining portions of  
 7 Dr. Lindsley's opening report?  
 8 MS. PIPER: Objection. Outside the  
 9 scope of what Dr. Trout was asked to  
 10 consider.  
 11 A. I didn't look at it to the extent that  
 12 I could analyze whether I was qualified or not.  
 13 I -- I think that I'm qualified to give the  
 14 opinions that I gave in my report.  
 15 MR. BENSON: Okay. All right. And  
 16 in -- why don't we go ahead and -- we have  
 17 previously marked a binder here as the --  
 18 Trout Exhibit Number 1, and I will have the  
 19 court reporter hand that to you.  
 20 (Dr. Trout's expert report, including  
 21 exhibits, was marked Trout Exhibit 1 for  
 22 identification, as of this date.)  
 23 THE WITNESS: Thank you.  
 24 Q. And I will represent to you that this  
 25 is a copy of your expert report that you've

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provided in this case, along with the exhibits cited therein. But to -- to convince yourself that I am correct, why don't you go ahead and look at the report here, and let me know if you agree that that appears to be the report you provided in this case.

A. So I flipped through the report in Tab 1, and it looks like -- I mean, just on a high level it looks like my report.

Q. Okay. Now, you -- after providing your expert report, you are aware that Dr. Lindsley prepared a reply report in response to that, correct?

A. Yes.

Q. And did you have an opportunity to read that report?

A. Yes.

Q. Okay. And after reading that report, have any of the opinions expressed in your opening report or your response report changed?

A. No.

Q. Okay. Did you formulate any additional opinions based on your reading of Dr. Lindsley's reply report?

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A. No, not based on what was in my report. I mean, those are the opinions in my report, and so I stick to those opinions that I gave.

Q. Okay. Is there anything at all you would want to supplement today with respect to your own opinions that you've not shared with defendants?

A. Not at this point in time.

Q. Okay. Fair enough. All right.

So if I could direct you to your -- your expert report, paragraph 25, please. And this is the definition of a person of ordinary skill in the art.

Now, based on your report, you have an understanding, your own definition of a person of ordinary skill in the art is a little different from that presented by Dr. Lindsley, correct?

A. Yes, there's a little bit of a difference, and I discuss that in paragraph 27.

Q. Right. But basically -- my understanding from your report is, your opinions wouldn't change were you to adopt Dr. Lindsley's

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definition of a person of ordinary skill in the art, correct?

A. Yes.

Q. And now, with respect to your own opinion about a person of ordinary skill in the art, first you believe that such a person would have knowledge that would be possessed of an MD with several years of experience as an oncologist treating patients with CML, correct?

A. That's part of the -- the knowledge of that P-O-S-A.

Q. And for clarity, CML is an abbreviation for chronic myelogenous leukemia; is that correct?

A. That's my understanding.

Q. Okay. And for the court reporter, myelogenous is spelled M-Y-E-L-O-G-E-N-O-U-S. And I make no representations as to whether or not I'm pronouncing that correctly.

Do you have any experience with the treatment for CML?

A. No, not outside of just reading the documents in this case.

Q. Okay. So what was your understanding

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of CML prior to your engagement in this case?

A. I didn't have a -- a specific or detailed understanding. I knew broadly about Gleevec is one of the pharmaceuticals, but I didn't know much about CML per se.

Q. Okay. And what, if anything, did you know about Gleevec? Was it just generally that it was a medicine for treating CML?

A. Yes, that it's an important medicine for treating, you know, leukemia or cancer diseases.

Q. Now, did you review that portion of Dr. Lindsley's opening report wherein he talked about CML?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine on.

A. Yes, I reviewed his entire report.

Q. And I think the question was simply, you did review that portion. Is there anything about that, in reading about Dr. Lindsley's description of CML, that you disagreed with?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was opine -- was

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2 said to opine on.

3 A. I don't have any opinions about that  
4 part of the report.

5 Q. Okay. Okay. How did -- in this case,  
6 how did you gain your understanding of CML?

7 A. I gained my understanding from the  
8 '625 patent, I mean, to the extent that I have  
9 an understanding, and from just the background  
10 that I read in Dr. Lindsley's report and maybe  
11 in some of the other documents as exhibits. But  
12 I think that the main focus was the '625, a few  
13 of the papers, a few of -- in the exhibit -- my  
14 exhibits, and then Dr. Lindsley's report --  
15 reports.

16 Q. With respect to Dr. Lindsley's reply  
17 report, did you focus on any section other than  
18 that portion of his report that was replying to  
19 your own opinions?

20 MS. PIPER: Objection. Outside the  
21 scope of what Dr. Trout was asked to opine  
22 on.

23 A. I read the whole report, but, no,  
24 my -- I think your question was about focus. My  
25 focus was on the paragraphs and other parts

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2 related to my opinions.

3 Q. Okay. Okay. Returning very briefly  
4 to your definition of a person of ordinary skill  
5 in the art, it also includes the opinion that a  
6 person of skill in the art would have the  
7 knowledge of a person having a Ph.D. with  
8 several years of experience conducting research  
9 on inhibition of tyrosine kinases, correct?

10 A. Yes, that's one of the parts to the --  
11 to the definition, yes.

12 Q. Okay. What, if any, experience do you  
13 have conducting research on inhibition of  
14 tyrosine kinases?

15 A. None, except -- not doing research, I  
16 mean, just broad background reading from my  
17 general knowledge, but not specific experience  
18 doing research.

19 Q. Can you kind of describe to me what  
20 your background knowledge is of just, you know,  
21 inhibition of tyrosine kinases?

22 A. Yes. Well, I studied biochemistry as  
23 an undergraduate. I continued learning about  
24 cellular biology and protein biochemistry  
25 post-undergraduate, certainly as an independent

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2 researcher when I joined MIT on the faculty in  
3 1998, so I continued to gain knowledge in that  
4 area. And I understand and continue to learn  
5 about drug development and inhibition broadly so  
6 I have this kind of general understanding.

7 Q. So is it fair to say your  
8 understanding of the inhibition of tyrosine  
9 kinases is not specifically as it relates to the  
10 treatment of CML?

11 A. Yes, that's correct.

12 Q. What, if any, understanding do you  
13 have about the role of the inhibition of  
14 tyrosine kinases in the treatment for CML?

15 MS. PIPER: Objection. Outside the  
16 scope of Dr. Trout's opinion.

17 A. I just have broad understanding based  
18 on the background that I just described and the  
19 documents that I reviewed.

20 Q. So prior to your engagement in this  
21 case, did you have any understanding of how  
22 tyrosine kinases and/or their inhibition were  
23 implicated in CML therapy?

24 A. Again, just very broadly. Nothing  
25 specific about that, no.

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2 Q. All right. And lastly, your opinion  
3 regarding the knowledge of a person having  
4 ordinary skill in the art includes a person with  
5 a Ph.D. in medicinal chemistry, pharmacology, or  
6 a related field with several years of experience  
7 in drug development and formulation, correct?

8 A. Yes. Correct.

9 Q. Okay. Now, what, if any, experience  
10 do you have -- can you -- well, strike that.

11 Can you describe for me your  
12 experience in drug development and formulation  
13 generally?

14 A. Yes. As an undergraduate at MIT in  
15 the '80s, I worked on research related to  
16 processing of pharmaceuticals and also enzymatic  
17 catalysis. I went on to do a Ph.D. in chemical  
18 reactivity. And then when I joined the MIT  
19 faculty in 1998, I began an independent research  
20 program focusing on formulation -- well, say,  
21 drug development and formulation broadly. And  
22 so I have continued that research up till today.  
23 I can go into all levels of detail as you like.

24 Q. Your researches into drug development  
25 and formulation, are they aimed at specific

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2 chemical compounds? For example, you know,  
3 active pharmaceutical ingredients, for example?

4 A. Yes. To qualify that, the broad focus  
5 of my research is to develop new technologies  
6 related to drug development, formulation, and  
7 manufacturing. In doing that we work on  
8 specific pharmaceuticals, a range of  
9 pharmaceuticals.

10 Q. Just for clarity, how do you define  
11 the term "pharmaceutical"?

12 A. And you're talking about general, not  
13 in the specific context, like --

14 Q. Just generally --

15 A. -- talking about the patent but just  
16 generally?

17 Q. Yes. I think you said, you know, you  
18 do work on specific pharmaceuticals, a range of  
19 pharmaceuticals. So, you know, when you're  
20 using it just generally in that sense, what is  
21 your understanding of -- what is your definition  
22 of a "pharmaceutical" as you use it there?

23 A. In that particular sense I was  
24 addressing your question which I interpreted as  
25 a -- a specific API, or active pharmaceutical

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2 ingredient, so the active ingredient I guess in  
3 a formulation or outside of a formulation.

4 Q. So a medicinal drug, for example?

5 MS. PIPER: Objection to form.

6 A. I guess I would stick with the  
7 terminology that I used.

8 Q. Okay. Now, you'll agree with me a  
9 person of ordinary skill in the art, as you've  
10 defined it, would understand a pharmaceutical  
11 composition to include an API, or active  
12 pharmaceutical ingredient, right?

13 A. Yes.

14 Q. And a person of ordinary skill in the  
15 art would also understand a pharmaceutical  
16 composition could include one or more excipients  
17 as well, correct?

18 A. Yes. And, again, I want to qualify, I  
19 know that's a term that has specific  
20 implications in this case. And I understand  
21 we're just speaking broadly. So outside of the  
22 context of, let's say, a specific term in a  
23 claim, yes.

24 Q. Okay. So generally speaking, just to  
25 rehash, and, again, just speaking generally, a

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2 person of ordinary skill in the art, in your  
3 opinion, hearing the term "pharmaceutical  
4 composition" would think of an API and one or  
5 more excipients, right?

6 A. Yes, broadly speaking. Again, I --  
7 that seems to be a term that's a little bit more  
8 used in a legal context than, let's say, a  
9 technical context. But if I put it into a  
10 technical context, then, yes.

11 Q. So is it -- I'm -- just so I  
12 understand, is it -- are you saying that that  
13 term like a "pharmaceutical composition" isn't  
14 typically used in the art, like, the  
15 pharmaceutical arts or the drug development  
16 field? Or you're just saying that it's used  
17 both in a legal context here but also in a --  
18 I'm just trying to understand.

19 MS. PIPER: Objection to form.

20 A. So it can be used in both contexts.

21 Q. Okay.

22 A. In sort of my daily -- daily basis  
23 we -- or daily work we typically would talk  
24 about a drug product or a drug formulation.  
25 Composition or pharmaceutical composition can

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2 also be used. Just I know it tends to be used  
3 more in the legal context, and certainly in this  
4 case, so I wanted to make that clear.

5 Q. Okay. I appreciate that. Thank you.  
6 And I think I'm clear on that now.

7 Okay. So do you consider yourself to  
8 be a person having ordinary skill in the art  
9 based on your own definition?

10 A. And just to clarify, you're asking  
11 about the entire definition?

12 Q. Correct.

13 A. No. I think my skill is really  
14 focused on the third part of that definition.

15 Q. Okay. Let me direct you to paragraph  
16 42 of your report, please. Now, you've  
17 reproduced here the single claim of the '625  
18 patent, correct?

19 A. Yes.

20 Q. And that's as it appears in the patent  
21 itself, right?

22 A. Unless I've made any typos, yes.

23 Q. And so we agree that the compound that  
24 is referenced here in Claim -- Claim 1 of the  
25 '625 patent is bosutinib, correct?

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1 Trout - Confidential  
 2 MS. PIPER: Objection to form.  
 3 A. Yes, that's my understanding.  
 4 Q. Okay. And you don't disagree with  
 5 Dr. Lindsley in that regard, right?  
 6 MS. PIPER: Objection to form.  
 7 A. No. As far as I understand it, that's  
 8 correct.  
 9 Q. Okay. Now, I see here that -- well,  
 10 so the claim is, you know, giving -- you know,  
 11 replacing the actual chemical name with  
 12 bosutinib, the claim states, "A pharmaceutical  
 13 composition comprising a CML inhibiting amount  
 14 of the compound bosutinib."  
 15 Correct?  
 16 A. Yes.  
 17 Q. Okay. Now, looking at Footnote 1,  
 18 which is on the bottom of page 9, you observe  
 19 here, in your opinion, that the '625 patent uses  
 20 treating and inhibiting CML interchangeably.  
 21 You see that?  
 22 A. Yes.  
 23 Q. Okay. And in formulating your  
 24 opinions, did you also view treating CML and  
 25 inhibiting CML as interchangeable terms?

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 2 on.  
 3 A. I didn't formulate opinions  
 4 specifically on that.  
 5 Q. Okay. Okay. Now, you understand that  
 6 the term "pharmaceutical composition" in -- as  
 7 it appears in Claim 1 has been construed by the  
 8 Court, correct?  
 9 A. Yes.  
 10 Q. And you provided that construction in  
 11 your opinion at paragraph 29, correct?  
 12 A. Yes.  
 13 Q. Okay. And it is your understanding  
 14 the Court's construction of "pharmaceutical  
 15 composition" is, "A pharmaceutically acceptable  
 16 composition containing the specified compound  
 17 and one or more excipients."  
 18 Correct?  
 19 A. Yes.  
 20 Q. Okay. And in this construction, your  
 21 understanding of a -- "the specified compound"  
 22 is bosutinib, correct?  
 23 A. Yes.  
 24 Q. Okay. And --  
 25 A. Meaning -- sorry, just to qualify.

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1 Trout - Confidential  
 2 MS. PIPER: Objection. Outside the  
 3 scope of Dr. Trout's opinion.  
 4 A. That's what I included here in the  
 5 background as I understand it. Yes.  
 6 Q. Well, the question here is, did you  
 7 use that -- those terms interchangeably, or are  
 8 you simply observing that you believe that the  
 9 '625 patent does so?  
 10 A. I'm observing that I think the '625  
 11 patent does so.  
 12 Q. Okay. So what is your understanding  
 13 of what a CML inhibiting amount of bosutinib  
 14 would mean?  
 15 MS. PIPER: Objection. Outside the  
 16 scope of Dr. Trout's opinion.  
 17 A. I don't have an opinion on that.  
 18 Q. Okay. So for clarity, you don't have  
 19 an opinion as to -- well, let me ask you a  
 20 different question.  
 21 In formulating your opinions, what was  
 22 your understanding of what a CML inhibiting  
 23 amount of bosutinib meant?  
 24 MS. PIPER: Objection. Outside the  
 25 scope of what Dr. Trout was asked to opine

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 2 That's the other part of the -- that's another  
 3 element of the claim, right --  
 4 Q. That's correct.  
 5 A. -- yes.  
 6 Q. And so your understanding is when --  
 7 when the Court is -- in the Court's construction  
 8 when it says, "A pharmaceutically acceptable  
 9 composition containing the specified compound,"  
 10 it's your understanding based on the claim that  
 11 that specified compound in this context is  
 12 bosutinib, correct?  
 13 A. Yes, in the context of Claim 1 of the  
 14 '625, correct.  
 15 Q. And one or more excipients, right? Is  
 16 the last portion of this construction.  
 17 So what is your understanding of what  
 18 an excipient would be in the context of this  
 19 construction?  
 20 A. So I talk about that, for example, on  
 21 page 15 of my report, paragraph 53. I say,  
 22 "There are ingredients other than the active  
 23 ingredient," and then there's some, you know,  
 24 more qualification of that in the subsequent  
 25 paragraphs in terms of specific types of

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 2 specifications that they must meet.  
 3 Q. Now, you don't disagree generally that  
 4 TWEEN 80 is -- can be an excipient in a  
 5 pharmaceutical composition as -- as you've  
 6 defined excipients here, right?  
 7 MS. PIPER: Objection to form.  
 8 A. It can be an excipient. It has to  
 9 meet the kind of specifications that I discuss  
 10 here, a particular version of TWEEN 80, but it  
 11 can be.  
 12 Q. Okay. And, in fact, it's described in  
 13 the '625 patent as a possible excipient for  
 14 bosutinib compositions, correct?  
 15 A. And just to be clear, could you point  
 16 me to where you're referring?  
 17 Q. Yes, I can. Let me direct you to  
 18 Exhibit A.  
 19 Sorry, my computer is asking me if I'm  
 20 enjoying the iAnnotate app that I'm using right  
 21 now, so I had to take care of that and let it  
 22 know I was indeed enjoying it, so. It wouldn't  
 23 leave me alone about it.  
 24 So, I'm sorry, we were going to  
 25 Exhibit A, which -- in responding to their

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 2 inquiry.  
 3 Closed it for me.  
 4 Okay. So this is the '625 patent. Do  
 5 you recognize that?  
 6 A. I mean, looking at the first page it  
 7 looks like the '625 patent that I'm familiar  
 8 with, yes.  
 9 Q. Okay. So let's go to Column 4,  
 10 beginning at line 5, and let me know when you're  
 11 there.  
 12 A. I'm there.  
 13 Q. Okay. Now, this begins with, "The  
 14 compounds of the invention may be formulated  
 15 with conventional excipients such as a filler, a  
 16 disintegrating agent, a binder, a lubricant, a  
 17 flavoring agent, color additive, or a carrier."  
 18 Right?  
 19 A. Yes.  
 20 Q. And then here in this section various  
 21 types of excipients are described. Would you  
 22 agree with me on that?  
 23 A. Yes, in the subsequent part of that  
 24 paragraph.  
 25 Q. And if we go to that paragraph that

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 2 begins around line 27 in Column 4, do you see  
 3 that?  
 4 A. Yes.  
 5 Q. And here within this -- in this it  
 6 states that, "Detergents such as TWEEN 20 and  
 7 TWEEN 80 can be used in certain formulations of  
 8 the invention."  
 9 Correct?  
 10 A. Yes. I think you're referring to  
 11 lines 34 to 35 in that Column 4.  
 12 Q. Yes. Correct. Okay. So you will  
 13 agree with me that the patent itself identifies  
 14 TWEEN 80 as a pharmaceutical excipient that  
 15 could be used in bosutinib compositions,  
 16 correct?  
 17 A. Yes. And I emphasize that this is  
 18 within the context of the '625 patent --  
 19 Q. Okay.  
 20 A. -- which we're talking about  
 21 pharmaceutical compositions.  
 22 Q. Okay. Perfect.  
 23 Now, some other -- some other  
 24 excipients that are mentioned here generally,  
 25 so -- for example, if we go back up a little bit

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 2 further to line 17, wherein it states, "When  
 3 provided orally or topically."  
 4 Do you see that paragraph?  
 5 A. Yes. Yes.  
 6 Q. Okay. You know, it says: When  
 7 provided orally or topically some -- such  
 8 compounds would be provided to a subject by  
 9 deliver -- by delivery in different carriers.  
 10 And then it says, "Typically such carriers  
 11 contain excipients such as starch, milk, sugar,"  
 12 and then it goes on and identifies some others,  
 13 correct?  
 14 A. Yes.  
 15 Q. And you'll agree with me that dextrose  
 16 is a sugar, correct?  
 17 A. Yes.  
 18 Q. And dextrose is a well-known excipient  
 19 for use in pharmaceutical compositions, wouldn't  
 20 you agree?  
 21 MS. PIPER: Objection to form.  
 22 A. Well, I would say that dextrose is in,  
 23 for example, the Handbook of Pharmaceutical  
 24 Excipients. So I assume you're talking about  
 25 the timeframe of the '625 patent.

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2 Q. Correct.

3 A. So it was known as an excipient, for  
4 example, in the Handbook of Pharmaceutical  
5 Excipients in that timeframe.

6 Q. Okay. And you reference the Handbook  
7 of Pharmaceutical Excipients, correct?

8 A. Yes.

9 Q. Okay. And the Handbook of  
10 Pharmaceutical Excipients is -- you'll agree  
11 with me is a handbook that identifies various  
12 pharmaceutical excipients that can be used in  
13 pharmaceutical compositions, correct?

14 A. Well, I would say it's a handbook, so  
15 it has entries on a set of pharmaceutical  
16 excipients, including selective but important  
17 properties that the formulation scientist or  
18 someone interested would need to know for its  
19 use as an excipient, including reference to  
20 various specifications beyond what's in that  
21 handbook.

22 Q. Okay. Do you have any understanding  
23 as to whether or not excipients are identified  
24 in the Handbook of Pharmaceutical Excipients  
25 that have never been used in pharmaceutical

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2 compositions approved by FDA?

3 A. I haven't checked all the excipients.

4 Q. Okay.

5 A. I presume they have been used, but I  
6 haven't checked them one by one.

7 Q. And do you have any understanding as  
8 to whether or not dextrose itself has been used  
9 in formulations of drugs that have been approved  
10 by FDA?

11 A. By the date of the '625 patent I  
12 presume you're talking about.

13 Q. Yes.

14 A. I can't think of an example sitting  
15 here. I have no reason to think that it wasn't  
16 used in other formulations, but I can't think of  
17 an example.

18 Q. Are you aware of a database that FDA  
19 maintains that identifies excipients that have  
20 been used and approved in drug products  
21 previously?

22 MS. PIPER: Objection to form.

23 A. Yes, I know there's a list.

24 Q. And do you know what the name of that  
25 list is?

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2 A. Yes. It's called the GRAS list, I  
3 think is what you're talking about. At least  
4 that's what I'm thinking of.

5 Q. GRAS list?

6 A. Yes. It's a -- abbreviation for  
7 Generally Recognized As Safe.

8 Q. Do you have any understanding as to  
9 whether or not dextrose is identified as a -- an  
10 excipient in the GRAS list?

11 A. I didn't specifically look it up in  
12 the GRAS list.

13 Q. Would you expect it would be  
14 identified there, based on your experience and  
15 knowledge?

16 A. I would think it would be identified  
17 there, but one would have to check to confirm.

18 Q. Okay. How about TWEEN 80? Would you  
19 expect TWEEN 80 would be identified in the GRAS  
20 list as well, based on your experience and  
21 knowledge?

22 A. Yes, again, I would expect it. I  
23 didn't specifically check it as of this date, as  
24 of the date of the '625 patent.

25 Q. And I appreciate your clarifications

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2 but I will confirm for you, just to simplify  
3 things, that if I'm asking you a question about  
4 this -- something in -- being known in the art,  
5 I am referring to known as of the priority date  
6 of the invention. Okay?

7 A. Okay.

8 Q. So if I'm going to deviate from that,  
9 I'll let you know. Okay.

10 A. Okay.

11 Q. But, again, I do appreciate your --  
12 your being clear about that when I ask a  
13 question. It's helpful.

14 Now, other carriers that are  
15 identified in Column 4 of the '625 patent, for  
16 example, at line 14 are carriers such as water,  
17 correct?

18 A. Yes, water is identified there.

19 Q. Okay. And there's really no dispute  
20 that water is a common carrier for  
21 pharmaceutical compositions, right?

22 MS. PIPER: Objection to form.

23 A. Yes. I mean, certain water that has  
24 to meet specifications for it to be used in a  
25 pharmaceutical composition. But it's possible,

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yes.

Q. All right. Let's talk a little bit about various modes of administration the '625 patent identifies for the pharmaceutical compositions of the invention. And I will direct you now, again staying in Exhibit A, Column 3 and line 52.

Now, do you see here where it states that the compounds may be provided orally, by intralesional, intraperitoneal, and there are various modes of administration identified, correct?

A. Yes.

Q. Okay. And, again, one of those identified here at -- looks like line 53 is intraperitoneal, right?

A. Yes.

Q. And what is intraperitoneal?

A. It means delivery into the body cavity, so not into the blood system, circulatory system directly, for example.

Q. Okay. Is that often abbreviated as ip, little i, little p?

A. I've seen it abbreviated as such.

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Q. Okay. Now, what is your understanding, if you have any, of what form of compositions are typically administered ip, or intraperitoneal?

A. What do you mean by "form"?

Q. Sure. So, for example, powders, tablets, solutions, suspensions, you know, what form of composition are typically administered intraperitoneal?

A. And speaking just generally, I would think typically it would be injected, and so it would have to be some kind of liquid or suspension.

Q. Okay. You said "liquid" or "suspension." Are those, in your mind, different things?

A. Yes. A liquid in that context, it is more broad. Suspension is specifically a liquid with solid material in it.

Q. Okay. So is it fair to say then, based on that testimony, that liquid, in your mind, is more something that -- where all of the various excipients are in solution versus a suspension where some of those excipients are

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suspended in the liquid matrix?

A. Yes, that's what I was thinking of in general context. It might differ depending on the specific context in which it's used.

Q. Are there any other forms of compositions or -- or that you're aware of that are delivered intraperitoneal?

A. There's none that I'm aware of. Those are the broad categories. This is a big field. Lots of people do research. Someone may have -- pretty confident that people -- someone must have tried other different types of forms, but the ones I gave you I think would be generally the ones used.

Q. Okay. Great.

Now, in your own research, do -- do you have an opportunity to use laboratory animals in your research?

A. I do not use laboratory animals in my laboratory. I certainly work with other people who use them and review literature and the results of those as I need them, but I do not in my lab do animal research.

Q. Have you ever in your career or

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education had an opportunity to work with laboratory animals?

A. So personally I have not done experiments on laboratory animals. I have helped to design studies that were done on laboratory animals and interpret the results. But that was -- since '98 when I started my independent career, so I generally have students and technicians and other people do that kind of research.

Q. Okay. Have you ever had experience with other researchers who have been doing cancer studies in mice?

A. I may have. Nothing specific comes to mind. Wasn't -- wasn't a big project that I was working on.

Q. Okay. So I do appreciate that working with laboratory animals is not something that you yourself have done in your career, but do you have an understanding at all as to whether or not -- or as to how common it is to administer the compositions to mice intraperitoneally?

A. I don't know how common it is, no.



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2 Q. Okay. All right. Now, are you  
3 familiar with the Animal Welfare Regulations  
4 promulgated by the USDA?  
5 A. What do you mean by "familiar"? Just  
6 do I know about -- that they exist?  
7 Q. Yes.  
8 A. Yes.  
9 Q. Have you ever had an opportunity to  
10 review those regulations?  
11 A. No.  
12 Q. Okay. How about the Policy on Humane  
13 Care and Use of Laboratory Animals? Are you  
14 familiar with that policy?  
15 A. Using your definition of "familiar,"  
16 yes.  
17 Q. So you're aware of it?  
18 A. I'm aware of it, correct.  
19 Q. Have you ever had an opportunity to  
20 review that particular document?  
21 A. No.  
22 Q. Okay. So let's return for a moment to  
23 your report, and I want to return to the claim  
24 for one moment, and that's at 42.  
25 A. I'm there.

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2 example, correct?  
3 MS. PIPER: Objection to form.  
4 A. Well, I wouldn't say it that way. I  
5 think it's -- can -- it's more inclusive than  
6 humans, so it could be used for veterinary  
7 purposes.  
8 Q. Okay. All right. So your  
9 understanding is, it could be used for humans  
10 and veterinary purposes. And what's the basis  
11 of that understanding?  
12 A. The basis is the claim. And I  
13 understand that there was some discussion with  
14 the Court about whether it's limited to humans,  
15 and I understand that it's not.  
16 Q. Okay. So based on looking at the  
17 claim and that discussion with the Court, it is  
18 your understanding at least that the claims do  
19 contemplate pharmaceutical compositions for  
20 veterinary purposes, right?  
21 A. Yes.  
22 Q. Okay. And that would include animals  
23 such as mice, correct?  
24 MS. PIPER: Objection to form.  
25 A. It could if you're trying to treat

1 Trout - Confidential  
2 Q. Okay. Thank you.  
3 When I refer to "the claim," I'm  
4 thinking about the claim with the construction  
5 the Court has provided. Okay? So in other  
6 words, in -- you would substitute pharmaceutical  
7 composition with the construction the Court has  
8 provided. Okay?  
9 A. Okay.  
10 Q. For clarity. All right.  
11 Now, based on that claim, what, if  
12 any, understanding do you have as to whether the  
13 pharmaceutical compositions described therein  
14 are required to be acceptable for human use?  
15 A. Described therein you mean  
16 specifically in the claim?  
17 Q. In the claim, right.  
18 A. Not generally in the patent but in the  
19 claim?  
20 Q. Right.  
21 A. My understanding that it's not -- is  
22 that it's not limited to human use.  
23 Q. Okay. So it does contemplate  
24 pharmaceutically acceptable compositions that  
25 could be administered to laboratory animals, for

1 Trout - Confidential  
2 mice. I guess if you have a pet mouse, for  
3 example.  
4 Q. Okay. So let me -- tell me a little  
5 bit about what your understanding -- what you  
6 mean when you say "pharmaceutical compositions  
7 can be used for veterinary purposes."  
8 A. What I mean is that as a  
9 pharmaceutical composition, it's used to treat  
10 or to attempt to treat a kind of disease, and so  
11 that can be done for humans or for nonhuman  
12 animals, the latter being veterinary purposes.  
13 Q. Based on your experience, is it --  
14 strike that.  
15 Now, you'll agree with me that in the  
16 context of laboratory research using animals,  
17 animals are often being treated for diseases,  
18 correct?  
19 MS. PIPER: Objection to form.  
20 A. Well, it depends on the experiment,  
21 the laboratory experiment, and the purpose of  
22 the experiment.  
23 Q. So there are -- there are specific  
24 contexts, you will agree, wherein laboratory  
25 animals have disease or some sort of condition

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2 which is being treated in the lab using  
3 pharmaceutical compositions, right?  
4 A. As a hypothetical, that's certainly a  
5 possibility.  
6 Q. Well, that's an important part of drug  
7 research, isn't it --  
8 MS. PIPER: Objection --  
9 Q. -- using laboratory animals to see how  
10 a target API is able to treat laboratory  
11 animals, correct?  
12 A. That's one part of laboratory research  
13 involving animals.  
14 Q. But it's almost unheard of, isn't it,  
15 to have -- in the drug application process to  
16 actually have a research plan that doesn't  
17 involve treating laboratory animals with the API  
18 at some level, correct?  
19 MS. PIPER: Objection to form.  
20 A. I'm not quite sure I understand your  
21 question. You're talking about filings to  
22 regulatory authorities? Or --  
23 Q. So just the -- you know, in the  
24 context of pharmaceutical drug development,  
25 isn't laboratory research using animals -- it

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2 almost always involves the use of laboratory  
3 animals, right?  
4 MS. PIPER: Objection to form.  
5 A. There's quite extensive use of  
6 laboratory animals in different stages of, let's  
7 say, drug creation, if that's what you mean.  
8 Q. Yes. Okay. And oftentimes that use  
9 includes having animals that are used as models  
10 of a specific disease, correct? So -- let me  
11 strike that.  
12 Are you familiar with the use of  
13 xenografts in mice as a model for studying  
14 potential candidates for treating cancer?  
15 A. Yes.  
16 Q. And what is a xenograft?  
17 A. A xenograft is when you put in foreign  
18 tissue or foreign cells into an animal such as a  
19 mouse, laboratory mouse.  
20 Q. So, for example, tumor cells that  
21 might have been harvested from a human, correct?  
22 A. That's an example, correct.  
23 Q. Okay. And then -- and so often in  
24 xenograft studies, the tumor cells are injected  
25 into the mouse and then the tumor is allowed to

1 Trout - Confidential  
2 grow, correct?  
3 A. That's an example, correct.  
4 Q. Right. And in many contexts if the  
5 tumor is left untreated, it will result in the  
6 death of the animal; is that correct?  
7 A. Well, I wouldn't quite say it that  
8 way. In the type of experiments that you're  
9 talking about the objective is not to treat the  
10 animal but to perform experiments to -- whatever  
11 the -- broadly speaking, the experiment is meant  
12 to accomplish. It's not to treat the animal.  
13 Q. That wasn't my question. My question  
14 was, when the xenograft tissue is introduced  
15 into the animal and the tumor is allowed to  
16 grow, if the tumor isn't addressed, it will --  
17 the tumor will grow and result in death of the  
18 animal, correct?  
19 A. Well, you are just talking broadly. I  
20 mean, I guess it depends on the type of tumor  
21 and the type of research that's being done and  
22 the hypothesis that's being tested.  
23 Q. Okay. Well, based on your review of  
24 the prior art in this case, isn't it true that  
25 the xenograft studies that were performed in the

1 Trout - Confidential  
2 prior art resulted in tumors that left untreated  
3 were fatal to the mice?  
4 A. And just to be specific, you're  
5 talking about the -- what I call the Boschelli  
6 2001 reference?  
7 Q. That is an example of the prior art,  
8 yes, that's correct.  
9 A. Yeah, so in that reference so that is  
10 a study performed on laboratory mice in which,  
11 as you say correctly, there were xenografts  
12 performed on mice that were meant to be  
13 sacrificed.  
14 Q. Is it important that they were meant  
15 to be sacrificed?  
16 A. Yes.  
17 Q. Why is that important?  
18 A. Because -- and, again, if there's a  
19 specific place in that reference, we can talk  
20 about the specific place. But in general terms,  
21 the objective of Boschelli and coworkers was not  
22 to treat laboratory mice per se, but to test a  
23 variety of hypotheses and -- and to determine  
24 outcomes. And what's important about sacrifice  
25 is that either way, if the tumors went away or

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if they didn't go away, the mice were not to continue living.

Q. So, in your opinion, is the fact that they weren't intended to continue leaving relevant to whether or not the experiment was a treatment of the animal?

A. Yes. Living -- just to be clear, I think living -- I don't know how it came out. But -- so, yes, because, again, the objective wasn't to treat animals, to cure them from a disease, or to manage a disease. The objective was to do experiments, and they were going to die either way regardless of the outcome.

Q. In your opinion, the fact that they were going to die either way, is that relevant to the types of pharmaceutical excipients one would select for a composition?

A. Yes. Could be, yes.

Q. Why?

A. Well, I've opined in my report, we can go to the specific places, but there are different requirements depending on what you're intending to do with the animals. I have references, for example, of -- Wolff reference,

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which we can talk about if you're interested. But I discuss this in many paragraphs in my report.

Q. Okay. So when you say "there are different requirements depending on what you're intending to do with the animals," can you elaborate on that for me a little bit? And, yeah, feel free --

A. Yes.

Q. -- to go to your report and direct me to that specific paragraph.

A. So, for example, on page 21, and subsequent places in my report, starting paragraph 67, that's when I talk about the fact that there's the xenograft done, the mice did not have CML, Compound 31a, which is also bosutinib, was not being administered to provide a therapeutic benefit, and the animals were to be sacrificed after testing.

And I talk -- I mean, essentially, the bulk of the substance of my report is why what was used or not pharmaceutically acceptable compositions or a pharmaceutically acceptable composition.

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Q. And that's the heart of your opinion, right? That the composition of Boschelli wasn't a pharmaceutically acceptable composition, correct?

A. That's a major part of, I guess, the conclusion, and -- and I discuss in multiple pages and paragraphs why that's the case.

Q. Now, I understand that you've been engaged as an expert witness in patent litigation cases previously, correct?

A. Yes.

Q. And have you ever been asked to give an opinion about a claim that patent lawyers taught -- defined as a method claim?

A. I'm pretty sure the answer to that is yes. I'm not thinking of one specific claim as we speak, but I'm sure I have.

Q. Based on your experience, is the claim of the '625 patent a method claim?

A. That's a legal question. I really leave that to the lawyers. I mean, my opinion certainly focused on the science and the meaning within the context of the claim construction.

Q. Okay. Does -- do you have any

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understanding as to whether or not Claim 1 of the '625 patent requires treating CML with a pharmaceutically acceptable composition?

MS. PIPER: Objection. Outside the scope of what Dr. Trout was asked to opine on.

A. I don't have an opinion on that.

Q. Okay. All right. You did direct us to paragraph 67, so why don't we take a look at that, paragraph 67 of your report. And this is that section of your report wherein you are stating your opinions that the Claim 1 of the '625 patent is not anticipated by Boschelli 2001.

And Boschelli is spelled B-O-S-C-H-E-L-L-I, correct?

A. Well, this is really a -- a summary. I would say my whole report addresses that issue.

Q. Okay. Fair enough.

So at 67 here, you say, "Boschelli 2001 discloses a newly lab-synthesized compound that is tested in animal experiments."

Correct?

1 Trout - Confidential  
2 A. Yes.  
3 Q. That lab synthesized compound is  
4 bosutinib, correct?  
5 A. Yes, the Compound 31a.  
6 Q. Okay. All right. Compound 31a in  
7 Boschelli 2001 is bosutinib, right?  
8 A. That's the molecule, yes.  
9 Q. Okay. Next you say, "In those animal  
10 studies reported in Boschelli 2001, human CML  
11 tumor cells were introduced into laboratory  
12 mice, and the tumors were assessed after  
13 administration of Compound 31a."  
14 Correct?  
15 A. Yes, that's what I wrote.  
16 Q. Okay. And then you go on to say, "The  
17 mice did not have CML."  
18 And so first -- let's just focus on  
19 that for a moment. What do you mean when you  
20 say, "Mice did not have CML"?  
21 A. What I mean is that the mice were not  
22 being treated for CML. They didn't -- they  
23 weren't taken to the lab with CML. They were  
24 specifically given humor CML tumor cells to be  
25 experimented on.

1 Trout - Confidential  
2 CML tumor cells had been introduced, correct?  
3 Let me direct you to -- perhaps I can  
4 direct you to page 46 of your report.  
5 A. So I think that there were two  
6 different types of experiments which they call  
7 staged and unstaged and --  
8 MS. PIPER: Clarification. Paragraph  
9 46 or page 46?  
10 MR. BENSON: Paragraph 46.  
11 Q. Are you at paragraph 46?  
12 A. Yes.  
13 Q. Okay. All right.  
14 A. So in the experiments discussed at the  
15 top of 46, the -- the tumor cells were  
16 inoculated first.  
17 Q. And then they were allowed to reach  
18 15 percent of the body weight of the mouse,  
19 correct?  
20 A. Well, I mean, that's when -- I guess,  
21 as I have written here, that's when the  
22 experiment was ended.  
23 Q. Right. Okay.  
24 Well, let me -- and then there was an  
25 unstaged model, correct?

1 Trout - Confidential  
2 Q. So isn't CML characterized by a tumor,  
3 CML that -- the myelogenous tumor cells?  
4 MS. PIPER: Objection to form.  
5 Q. I mean -- I mean, that is what  
6 characterized the CML, right, having tumors that  
7 are cancerous?  
8 MS. PIPER: Objection. Outside the  
9 scope of Dr. Trout's opinion.  
10 A. I'll leave it to the medical doctors  
11 to answer that question.  
12 Q. So you don't disagree that human CML  
13 tumor cells were introduced into the laboratory  
14 mice, correct?  
15 A. Correct.  
16 Q. Okay. And that those CML tumor cells  
17 were allowed to proliferate in the mice,  
18 correct?  
19 A. Well, there were different types of  
20 experiments but broadly speaking, I would say  
21 the cells were introduced, and the effects of  
22 various compounds on those cells were tested, in  
23 particular bosutinib.  
24 Q. And -- right. And so bosutinib was  
25 administered to these mice after they had -- the

1 Trout - Confidential  
2 A. Yes.  
3 Q. Okay. And then you write here that,  
4 "Boschelli 2001 concluded Compound 31a  
5 effectively inhibited tumor growth."  
6 Correct?  
7 A. Yes, I'm just quoting from Boschelli.  
8 Q. And you don't disagree with that  
9 conclusion, correct?  
10 MS. PIPER: Objection. Outside the  
11 scope of Dr. Trout's opinion.  
12 A. I don't have an opinion. I'm just  
13 quoting -- this is background on Boschelli, and  
14 I'm just quoting Boschelli here.  
15 Q. Okay. So you didn't independently  
16 assess whether Compound 31 did or did not  
17 inhibit tumor growth in this model, correct?  
18 MS. PIPER: Objection. Outside the  
19 scope of Dr. Trout's opinion.  
20 A. That's correct.  
21 Q. Do you have any reason to disagree  
22 with the conclusions of Boschelli?  
23 MS. PIPER: Objection. Outside the  
24 scope of Dr. Trout's opinion.  
25 A. I don't have any reason to agree or

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2 disagree. I'm just providing quotes of  
3 background from Boschelli. I didn't analyze  
4 that separately.  
5 MR. BENSON: Okay. Okay. Do you want  
6 to take a -- is this a good time for a  
7 short break?  
8 THE WITNESS: Sure. If you want to  
9 keep going, we can keep going. If you want  
10 to take a break --  
11 MR. BENSON: Yeah, I could use a  
12 break.  
13 THE VIDEOGRAPHER: The time is  
14 10:14 a.m., and we are going off the  
15 record.  
16 (Recess from 10:14 to 10:28.)  
17 THE VIDEOGRAPHER: The time is  
18 10:28 a.m., and we are back on the record.  
19 Q. Okay. All right. Let's return to  
20 paragraph 46. And this is, again, just your --  
21 you know, kind of just articulation of what you  
22 see in Boschelli, correct?  
23 A. Well, it's part of the background in  
24 Boschelli.  
25 Q. Yeah. Okay. All right. Now, so

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2 setting aside for the moment -- so the vehicle  
3 we see here that you describe at paragraph 46, I  
4 think it's the second -- no, third full  
5 sentence, you're quoting, and it says, "The  
6 vehicle used was 2 percent TWEEN 80 and  
7 5 percent dextrose/water."  
8 You see that?  
9 A. Yes, that's part of the quote.  
10 Q. Okay. Now, setting aside the  
11 pharmaceutical grade of excipients used, you  
12 don't disagree that that describes a  
13 pharmaceutical vehicle that could be used with  
14 an API in the context of -- as that would be  
15 described in the invention?  
16 MS. PIPER: Objection to form.  
17 A. I'm sorry, just to be clear, you're  
18 asking a hypothetical outside of the Boschelli?  
19 Q. Let me ask a different question.  
20 Okay. Now, do you recall in Dr. Lindsley's  
21 report he gives the opinion that 3 milligrams of  
22 bosutinib, 10 milligrams TWEEN 80, and 25  
23 milligrams of a dextrose/water mixture was  
24 placed in a .5 milliliter aqueous vehicle? Do  
25 you remember that testimony?

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2 A. Maybe we could go to his report. I  
3 remember something like that, but I haven't  
4 memorized his report.  
5 MR. BENSON: Do we have a copy of his  
6 report?  
7 Here you are.  
8 MS. PIPER: Thank you.  
9 MR. BENSON: I don't know if there  
10 are -- Alembic, if there are portions of it  
11 that are -- there might be portions of it  
12 that address the infringement position with  
13 respect to Sun, so you might want to --  
14 MS. WEISBRUCH: And if I need to step  
15 outside the room, that's fine, too.  
16 MR. BENSON: No, that's fine. It's  
17 just that it might be in the binder so --  
18 MS. BEIS: The report itself was  
19 submitted on behalf of both Sun and Alembic  
20 so --  
21 MR. BENSON: Yeah, but there might  
22 be -- I think there's a section --  
23 MS. BEIS: We will let you know if  
24 something comes up.  
25 MR. BENSON: I'm not going to be

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1 Trout - Confidential  
2 directing you to any of those portions.  
3 MS. WEISBRUCH: If I need to step out,  
4 just let me know.  
5 MR. BENSON: Sorry, just protective  
6 order issues.  
7 Can I have this marked as the Trout  
8 Deposition Exhibit Number 2, please.  
9 (Opening expert report of Craig W.  
10 Lindsley, Ph.D. and reply expert report of  
11 Craig W. Lindsley, Ph.D. were marked Trout  
12 Exhibit 2 for identification, as of this  
13 date.)  
14 THE WITNESS: Thank you.  
15 MR. BENSON: Okay. Did I hand you a  
16 copy, Counsel? I did. Okay. Thank you.  
17 Sorry.  
18 MS. PIPER: Thank you.  
19 Q. I've handed you -- the court reporter  
20 has handed you what we've marked as Trout  
21 Deposition Exhibit Number 2, and this is a  
22 binder that contains two documents tabbed 1 and  
23 2. The first is the opening expert report of  
24 Dr. Craig Lindsley and the second is the reply  
25 expert report of Dr. Lindsley.

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Could you please just briefly take a look at those two documents and confirm these are the expert reports of Dr. Lindsley that you have reviewed in connection with your work in this case.

(Witness reviewing document.)

A. Okay. I've flipped through these, they're over a hundred pages, and they look like the two reports that I reviewed.

Q. Okay. Thank you very much.

I will direct you to the first tab, which is the opening report of Dr. Lindsley. And in particular, I would like you to go to -- paragraph 161 and 162 is where we will be.

MS. PIPER: One clarification. This entire binder is Trout Exhibit 2, both reports?

MR. BENSON: Yes.

MS. PIPER: Thank you.

MR. BENSON: You're welcome.

A. Without the exhibits?

Q. That's correct.

A. Okay. I'm at paragraph 161 and 162.

Q. Okay. Now, this is that part of

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Dr. Lindsley's report wherein he opines the Claim 1 of the '625 patent is invalidated as anticipated by Boschelli 2001, right?

A. Yes. And that's the heading in the -- the previous page 57, section Roman numeral IX.

Q. And these are the specific opinions you're responding to in your own expert report, correct?

MS. PIPER: Objection to form.

A. I mean, I -- I think -- I'm responding generally -- in general terms to the opinions in his report, or maybe other location, I wouldn't say it's limited. But this is certainly the section in which he opines that the patent is invalid or Claim 1 of the patent is invalid.

Q. Just so -- the avoidance of any ambiguity moving forward, the only opinion of Dr. -- well, Dr. Lindsley has provided a number of opinions about the invalidity of the '625 patent, correct?

A. Yes.

Q. And one of those opinions, speaking in the broadest sense, is that Claim 1 of the '625 patent is anticipated and therefore invalid,

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correct?

A. Correct. That's one of Dr. Lindsley's opinions.

Q. And that is the sole opinion to which you are responding to in this case, correct?

A. Yes, that's correct. Specifically anticipation due to the Boschelli 2001 document.

Q. Correct.

A. Correct.

Q. Okay. I just wanted to be sure, any of his other opinions about the '625 patent being invalid for written description, for example, you're not opining on that particular aspect of his report, correct?

A. Correct.

Q. And his opinions about enablement or any section -- well, any of the section 112 arguments he is making in his report, you're not responding to those particular arguments, correct?

A. Counsel, that sounds like a legal term. I'm solely responding to anticipation due to Boschelli 2001.

Q. Okay. All right. Yeah. I think

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that's clear. Thank you.

All right. So let's return to paragraph 161, and in this particular paragraph, second sentence, Dr. Lindsley is -- is stating his understanding of Boschelli 2001 as disclosing, "Xenograft studies wherein bosutinib was dosed ip in amounts up to 100 milligrams per kilogram as a 0.5 milliliter solution prepared in 2 percent TWEEN 80, 5 percent dextrose/water."

Do you see that?

A. Yes, I see that written here.

Q. Do you disagree with Dr. Lindsley in that regard?

A. Well, I don't disagree that -- that Boschelli states that. I mean, Boschelli is doing a lot more than just that, and other amounts, too. But there's nothing wrong with that sentence if one understands that it's part of a broader context.

Q. Right. Okay. And then the next -- the next paragraph 162, Dr. Lindsley concludes, "Thus, Boschelli 2001 discloses a composition comprising approximately 3 milligrams bosutinib,

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 2 10 milligrams TWEEN 80, and 25 milligrams  
 3 dextrose/water in a .5 milliliter aqueous  
 4 vehicle."  
 5 Do you see that?  
 6 A. Yes. And just to be clear, you --  
 7 actually I think the way you said it is probably  
 8 better because you didn't read the "and enables"  
 9 so --  
 10 Q. Yeah, I didn't want to get -- yeah, I  
 11 just wanted you to focus on the composition that  
 12 he describes. Okay?  
 13 A. Yes. Okay.  
 14 Q. And we'll get back to the enabled  
 15 part.  
 16 But do you disagree with Dr. Lindsley  
 17 that the composition disclosed in Boschelli is  
 18 as stated here in paragraph 162?  
 19 A. Well, Dr. Lindsley seems to be basing  
 20 that on certain assumptions and calculations.  
 21 I -- I didn't try to reproduce those  
 22 calculations or determine whether his  
 23 assumptions are valid or not. But I can take  
 24 what he's written here and discuss it.  
 25 Q. Okay. Well, you haven't disagreed

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 2 calculations.  
 3 Q. Okay. And we can agree just for --  
 4 just broadly speaking, setting aside whether or  
 5 not any of the excipients used in Boschelli were  
 6 pharmaceutical grade excipients, we can agree  
 7 that Boschelli discloses compositions containing  
 8 bosutinib, correct?  
 9 A. Compositions as such, Boschelli does  
 10 not call them pharmaceutical compositions. But  
 11 if you mean compositions broadly, then, yes.  
 12 Q. Yes. And those compositions disclosed  
 13 in Boschelli are compositions containing  
 14 bosutinib as the API, correct?  
 15 A. Well, again, API means active  
 16 pharmaceutical ingredient. The bosutinib is  
 17 designated as Compound 31a in Boschelli. And  
 18 again -- and I elaborate my opinions in my  
 19 report, but it's not being used as a  
 20 pharmaceutical here. So I wouldn't use it as  
 21 an -- I wouldn't characterize it as an API, and  
 22 I don't think Boschelli does either.  
 23 Q. What would you characterize bosutinib  
 24 in this composition? What is it?  
 25 A. It's a -- a chemical that was

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 2 with it in your own responsive report, correct?  
 3 MS. PIPER: Objection to form.  
 4 A. I -- I don't think that I -- well, I  
 5 don't remember specifically. I would have to  
 6 look through my report. But I know I did not  
 7 reproduce his calculations or attempt to  
 8 validate his assumptions in my report, or in my  
 9 activity in this case.  
 10 Q. Okay. Do you have any reason, as you  
 11 sit here today, to disagree with Dr. Lindsley  
 12 with respect to his conclusions here at  
 13 paragraph 162 as to the composition components?  
 14 A. I don't have a reason to disagree or  
 15 to agree with his 3 milligrams of bosutinib  
 16 calculation, except that he seems to take only  
 17 one of the concentrate -- one of the amounts of  
 18 dosing used by Boschelli 2001.  
 19 Q. Okay.  
 20 A. There are others there, too.  
 21 Q. Okay. Well, it's fair to say you  
 22 don't independently come up with your own  
 23 calculations with respect to the compositions  
 24 disclosed in Boschelli, correct?  
 25 A. That's correct. I did not do my own

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 2 synthesized and tested to -- in a series of  
 3 experiments to determine its effects on various  
 4 cells and other assays.  
 5 Q. Okay. You don't disagree bosutinib  
 6 is, in fact, an active pharmaceutical  
 7 ingredient, right?  
 8 MS. PIPER: Objection to form.  
 9 A. I don't disagree that it is today.  
 10 Q. So do you disagree that at the time of  
 11 Boschelli that bosutinib was an active  
 12 pharmaceutical ingredient?  
 13 A. I -- I don't know if I've specifically  
 14 opined upon that. I mean, I know that it's not  
 15 used as a pharmaceutical. Let's put it that  
 16 way. And -- and to me sitting here and trying  
 17 to answer your question, an active  
 18 pharmaceutical ingredient has to have a  
 19 pharmaceutical effect.  
 20 Q. When --  
 21 A. I don't think -- and I don't think  
 22 that's -- the objective was not to have a  
 23 pharmaceutical effect per se in Boschelli. It  
 24 was to study the effect of a variety of  
 25 different synthesized chemicals including 31a,

1 Trout - Confidential  
 2 which we can call bosutinib.  
 3 Q. What -- when you say "pharmaceutical  
 4 effect," what does that mean to you?  
 5 A. It means -- or we could use the term  
 6 "pharmaceutical activity." It means to me that  
 7 it's used to treat, let's say, patients of  
 8 whatever sort. I don't mean that it has to be  
 9 commercialized. It could be earlier than that.  
 10 Q. So is it -- is your definition  
 11 intentional? In other words, when it's being  
 12 administered, one has to intend it to have a  
 13 specific effect? Is that what you're  
 14 suggesting?  
 15 A. I don't think I'm suggesting that it's  
 16 intentional, that it's -- intentionality. I  
 17 think -- I mean, it depends what you mean. It  
 18 has to be administered in a certain context, so  
 19 in that way maybe there's an intentionality in  
 20 choosing the context.  
 21 Q. So the compound described in Boschelli  
 22 is bosutinib, correct, the Compound 31a? I  
 23 mean, we've already established that, right?  
 24 A. Yes.  
 25 Q. All right. And chemically it's the

1 Trout - Confidential  
 2 same bosutinib as is currently marketed in  
 3 the -- in the drug Bosulif I believe is the --  
 4 yeah, Bosulif, correct?  
 5 A. Yes, that's my understanding.  
 6 Q. Okay. So the identity of the actual  
 7 chemical entity is -- is no different in  
 8 Boschelli than it is in the marketed drug  
 9 Bosulif, right?  
 10 MS. PIPER: Objection to form. And  
 11 also objection. Outside the scope of  
 12 Dr. Trout's opinion.  
 13 A. I mean, it -- again, I'm not sure  
 14 maybe what you mean by "chemical entity." I  
 15 think maybe I -- if I understand your question  
 16 correctly, what I have opined upon is that the  
 17 31a as it synthesized and with the impurity  
 18 levels, and whatnot, is not an API as such,  
 19 something that would go into a -- a -- a  
 20 pharmaceutically acceptable composition.  
 21 Q. The -- an active pharmaceutical  
 22 ingredient, so to the -- let me strike that.  
 23 To the extent we're talking about  
 24 bosutinib as an active pharmaceutical  
 25 ingredient, we're talking about the chemical

1 Trout - Confidential  
 2 compound bosutinib, correct?  
 3 A. No, I think we're talking about the  
 4 compound -- well, there were two different  
 5 contexts, and maybe we're talking at cross  
 6 purposes. But active pharmaceutical ingredient,  
 7 API, uses pharmaceutical, so it seems to me that  
 8 it's more than just a chemical. There's  
 9 something more behind it than just that. If you  
 10 want to define it as such, you know, we can talk  
 11 about it in those terms.  
 12 Q. Did the inventors do -- in this --  
 13 in -- did the inventors of the '625 patent do  
 14 anything to the chemical compound bosutinib that  
 15 was different than -- or that rendered it to be  
 16 a pharmaceutical wherein in Boschelli it was  
 17 not?  
 18 MS. PIPER: Objection. Outside the  
 19 scope of Dr. Trout's opinion.  
 20 A. I didn't opine on that question.  
 21 Q. So I'm trying to understand, I guess,  
 22 how bosutinib is a pharmaceutical now but it was  
 23 not a pharmaceutical in Boschelli. And can you  
 24 help me understand your opinions in that regard?  
 25 A. Yes. For example, we can look at my

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 2 report pages 14 and 15, paragraphs 51 and 52, in  
 3 which a defined active pharmaceutical  
 4 ingredient, component of a pharmaceutical  
 5 composition, and -- and it goes on. And I -- I  
 6 think as a summary, an important part is that  
 7 the API has to meet certain specifications.  
 8 And I should say, there are other  
 9 parts of my report in which I discuss this.  
 10 This is one part, right? You can go to the  
 11 other parts if you want.  
 12 Q. All right. So I understand your  
 13 opinion that -- I understand your opinion that  
 14 the bosutinib in Boschelli was not  
 15 pharmaceutically acceptable as you use that  
 16 term, correct? That's your opinion?  
 17 A. My opinion is that it's likely not.  
 18 It was not characterized as such, and so it's  
 19 likely not.  
 20 Q. Okay. That's fair. Thank you.  
 21 But you're -- you're not saying that  
 22 bosutinib itself doesn't have the very same  
 23 activity in inhibiting, for example, Src kinase,  
 24 tyrosine kinase, as it does in the marketed  
 25 product Bosulif, right?



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 2 MS. PIPER: Objection. Outside the  
 3 scope of Dr. Trout's opinion.  
 4 A. I haven't opined on the activity of  
 5 this drug per se, or the activity of a compound,  
 6 or -- or whatnot.  
 7 Q. You don't disagree that Boschelli  
 8 concluded by administering the composition that  
 9 contained bosutinib, they were able to inhibit  
 10 tumor growth in the mice they studied, right?  
 11 MS. PIPER: Objection. Outside the  
 12 scope of Dr. Trout's opinion.  
 13 A. I think, as we discussed, I quoted  
 14 Boschelli in background, for example, paragraph  
 15 46. I didn't independently analyze that.  
 16 Q. But you are testifying today that the  
 17 bosutinib in Boschelli is not a pharmaceutical;  
 18 is that right?  
 19 MS. PIPER: Objection to form.  
 20 A. It's -- it's -- well, it's not a  
 21 pharmaceutical composition.  
 22 Q. Okay. So the -- the composition which  
 23 included bosutinib, TWEEN 80, dextrose, and  
 24 water, your opinion is, that is not a  
 25 pharmaceutical composition; is that right?

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1 Trout - Confidential  
 2 MS. PIPER: Objection. Outside the  
 3 scope of Dr. Trout's opinion.  
 4 A. I don't think I have in my report an  
 5 opinion about that.  
 6 Q. Okay. So if -- if the -- if the --  
 7 can we just agree that whether it's a  
 8 pharmaceutical composition or not, that  
 9 Boschelli, in fact, discloses a composition,  
 10 correct?  
 11 A. Yes, we can call it a composition.  
 12 Q. Okay. So the composition of  
 13 Boschelli, had they included purity information  
 14 as to the bosutinib, would that change your  
 15 opinion as to whether or not the composition of  
 16 Boschelli was a pharmaceutical composition?  
 17 A. So it depends on the details of this  
 18 hypothetical. I mean, I would have to go  
 19 through what their disclosure would be. I mean,  
 20 there's -- that's not the sole reason. I have a  
 21 whole variety of reasons which led me to this  
 22 opinion.  
 23 Q. Okay. So one of the other reasons, in  
 24 your opinion, was that there was no indication  
 25 in Boschelli that the excipients used were

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 2 (Witness reviewing document.)  
 3 A. I -- I think a better way of saying is  
 4 what -- what I opined is, for example, on  
 5 page 25, paragraph 77, "There is no indication  
 6 in Boschelli 2001 of pH control in the disclosed  
 7 TWEEN 80, dextrose/water solution," that's one  
 8 aspect. And I talk about various, let's say,  
 9 lacks of indication. So there's no indication  
 10 that what we are discussing is a pharmaceutical  
 11 composition and for a variety of reasons.  
 12 Q. Okay. The question I have then is, as  
 13 you sit here today, is it your opinion that the  
 14 Boschelli composition is not a pharmaceutical  
 15 composition?  
 16 A. My opinion -- and, again, there's a  
 17 lot in my report that gets here -- is that  
 18 there's no indication that it discloses a  
 19 pharmaceutical composition for -- for a variety  
 20 of reasons that I mention here.  
 21 Q. Does the fact that the composition was  
 22 administered ip to mice for the purposes of  
 23 inhibiting tumor cell growth any indication to  
 24 you as to whether or not it was a pharmaceutical  
 25 composition?

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 2 pharmaceutical grade, correct?  
 3 A. That's correct.  
 4 Q. So --  
 5 A. If -- just to be clear, that's  
 6 another -- there's a variety.  
 7 Q. Yeah. So let's say a hypothetical  
 8 that Boschelli disclosed that the bosutinib was  
 9 pure and that the excipients used were  
 10 pharmaceutical grade excipients. Would that  
 11 then change your opinion as to whether or not  
 12 Boschelli disclosed a pharmaceutical  
 13 composition?  
 14 A. Well, I would need to -- certainly  
 15 that would affect -- if the excipients were  
 16 disclosed as pharmaceutically acceptable, that  
 17 would certainly affect my analysis. I'm not  
 18 sure what "purity" means in -- in the context of  
 19 your question. I mean --  
 20 Q. Well, one of the issues you took with  
 21 the bosutinib was that it hadn't been purified  
 22 to the degree one would expect of a -- an API  
 23 that is going to be incorporated in a drug for  
 24 use in treating patients, right?  
 25 A. Yes. Purity is a -- was a significant

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issue, for example, on my paragraph 70.

Q. Okay. So let's say that the bosutinib was pure, and the excipients used in the Boschelli composition were pharmaceutical grade excipients. Now, with that information, would your opinion change as to whether or not the composition of Boschelli is a pharmaceutical composition?

A. And, Counsel, I'm not trying to split hairs but it's -- I think saying that a compound is pure is a little more complicated. So it has to be characterized and the -- the impurity profile needs to be characterized. If you're telling me that it was characterized and there was no detectable impurities, then that would -- I would have -- have to redo my analysis --

Q. Okay.

A. -- based on that.

Q. Okay.

A. It would be very unusual if that were the case.

Q. Well, let's say that is the case. Let's say it is pure bosutinib, and the excipients in the formulation were

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pharmaceutical grade excipients. With that hypothetical, how would that change your opinion as to whether or not the composition in Boschelli was a pharmaceutical composition?

MS. PIPER: Objection to form.

A. I would have to go through -- I mean, I list a whole variety of other issues. But that would change my set of opinions in the sense that those two opinions, again, with purity being -- it was characterized in an adequate way for a pharmaceutical, I would have to take that into account in a reanalysis.

Q. Okay. But you haven't -- you haven't considered that in -- as you sit here today, you haven't considered that -- how those factors would change your opinion. Is that fair?

A. Well, I've considered them broadly in the sense that I considered what was necessary for something to be a pharmaceutical composition and what the disclosure in Boschelli 2001 was. So I considered them in that broad sense. I didn't do an -- before today do an exercise in the specific hypothetical.

Q. So you'll agree with me Boschelli

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doesn't disclose -- well, strike that.

You'll agree with me the excipients used in the Boschelli experiments weren't identified as non-pharmaceutical grade excipients, right?

MS. PIPER: Objection to form.

A. That's right. They -- their source was not identified at all. And so they weren't explicitly identified as non-pharmaceutical versions. But I think the skilled person would expect that if they were pharmaceutical compositions, that would be disclosed.

Q. Why is that?

A. Because it means that there was a -- a specific grade that was used, and there was -- there would be specific attention paid to that. The researchers in Boschelli did not pay specific attention to the type of -- call them excipients used.

Q. Are you saying they didn't pay attention to it, or they simply didn't disclose it in their paper?

A. Well, I mean, pay attention to it in the sense of bringing attention to it, let's

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say, disclosing it to the reader of this paper, if you want to say it that way.

Q. But wouldn't a person of ordinary skill in the art who is familiar with animal studies expect that the excipients were pharmaceutical grade excipients?

MS. PIPER: Objection to form.

A. I think I've given a variety of opinions in which person, let's say, would not necessarily expect from the disclosure in Boschelli, and specifically, there's a reference from an author named Wolff which talks about the fact that they could very well be non-pharmaceutical grade.

Q. But doesn't Wolff disclose that the default is that it -- that excipients should be pharmaceutical grade excipients, absent some extenuating circumstances?

MS. PIPER: Objection to form.

Q. And if you would like to go to Wolff, we can do that.

A. Yes, that would be great.

Q. Let's go to -- this is going to be Exhibit T, as in Tom, in your report.

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2 And -- you have that?

3 A. Yes, I'm there.

4 Q. Okay. Is this the Wolff reference  
5 you're referring to?

6 A. Yes.

7 Q. Okay. All right. And I believe the  
8 specific section you were addressing is on -- if  
9 you look at the bottom left-hand corner of the  
10 Wolff reference, there is a page number. And  
11 I'm looking at page 34. Are you there?

12 A. Yes.

13 Q. And your opinion focuses on the  
14 question in the middle column of Wolff. It's  
15 the third question, and it states, "Are the  
16 scientists at our institution allowed to use  
17 non-pharmaceutical grade chemical compounds in  
18 physiological preparations involving laboratory  
19 animals?"

20 Right? That's the question?

21 A. Yes. And then there's another  
22 sentence after that but that's --

23 Q. Okay. And then it -- right. So let's  
24 focus on that part of it first. And so it's  
25 your opinion that Wolff -- and I think the part

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2 that you focused on is that Wolff recognized  
3 that under certain circumstances the use of  
4 non-pharmaceutical grade excipients is allowed,  
5 right?

6 A. Well, I mean, the second sentence in  
7 the query is probably important because it also  
8 differentiates survival versus non-survival  
9 experiments. But the way Wolff answers it in  
10 his first sentence that you're referring to,  
11 alluding to that it's allowed but specifically  
12 saying, "It's a necessary and acceptable  
13 component of biomedical research."

14 Q. Okay. So -- but doesn't -- but Wolff  
15 goes on to say that, "The use of  
16 non-pharmaceutical grade excipients should be  
17 based on, 1, scientific necessity, 2,  
18 nonavailability of an acceptable veterinary or  
19 human pharmaceutical grade compound, and, 3,  
20 specific review and approval by the IACUC."

21 Correct?

22 A. Yes.

23 Q. All right. Now, do you see anything  
24 in Boschelli that would lead you to believe that  
25 there was a scientific necessity to use

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2 non-pharmaceutical grade TWEEN 80 and dextrose?

3 A. Well, I would say it the other way  
4 around. There was not a scientific necessity  
5 for Boschelli to use pharmaceutical grade  
6 compounds. So I think that's the way I would  
7 address Number 1 here.

8 Q. Isn't -- I mean, when scientists are  
9 doing research involving laboratory animals,  
10 isn't the fact that these are living creatures  
11 reason enough in a scientific justification for  
12 using pharmaceutical grade excipients in things  
13 being administered to those animals?

14 A. No. I think that's exactly the point  
15 of the Wolff reference. Again, these animals  
16 were specifically induced with cancer with the  
17 intention of studying the effect of chemical --  
18 chemicals on cancer, with the intention that no  
19 matter what they were to be sacrificed.

20 Q. So under those circumstances it didn't  
21 matter whether it was pharmaceutical grade  
22 excipients. Is that your testimony?

23 A. My testimony is that there's no  
24 indication that pharmaceutical excipients were  
25 used, and there was not a necessity that

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2 pharmaceutically acceptable excipients were  
3 used. And, again, that's just part of my  
4 opinion. The composition and the chemical  
5 itself are other parts of it. But if we're just  
6 focused on the excipients...

7 Q. But here the use of non-pharmaceutical  
8 excipients has to be based on scientific  
9 necessity, not the use of pharmaceutical  
10 excipients, correct?

11 MS. PIPER: Objection to form.

12 A. Well, I mean, my reading of it is, is  
13 it necessary to use non-pharmaceutical? Is it  
14 necessary to use pharmaceutical? One would -- I  
15 think you have to look at this in a broader --  
16 in the broad way in which the authors Wolff, et  
17 al., are trying to address this.

18 Q. Did you talk to any of your colleagues  
19 who do scient -- who do animal research to  
20 determine what their standard practice would be  
21 with respect to the use of pharmaceutical versus  
22 non-pharmaceutical grade excipients?

23 A. No.

24 Q. Okay. Well --

25 A. And I mean, just to be clear,

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specifically in this case and specifically in that way.

Q. Right.

A. I've certainly talked to colleagues outside of this case and before about animal studies and what they use.

Q. You've had discussions about that specific issue, about whether they use pharmaceutical grade or non-pharmaceutical grade excipients in compositions they're administering to animals?

A. I have not specifically posed that question. I just had general discussions.

Q. Okay. So what is the basis of your understanding that a person of ordinary skill in the art reading Boschelli would not understand the excipients to be pharmaceutical grade excipients?

A. Again, my opinion is that there's not an indication that they're pharmaceutical grade excipients, and that's based on -- I mean, there's a variety of reasons in my report. But if you want me just to summarize, I mean, I would take my opinions as a whole in the report.

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But a couple of those opinions are that there's no specific disclosure that they're pharmaceutical grade. Also, there's no scientific necessity because these are experiments that are done early on in the discovery phase in which the animals are induced with the cancer and meant to be sacrificed.

Q. Okay. So this idea that the animals are meant to be sacrificed, can you just explain -- and I know that you've -- you've talked generally about that, but how is that important for your opinion that the Boschelli composition was not a pharmaceutical composition?

A. Because the animals are not being treated per se to cure a disease. They're being studied for the effects of various compounds and -- in various assays including the xenograft study. And so the idea is not to treat them. The idea is to study and then sacrifice them regardless of the outcome. So -- yeah, stop there.

Q. Okay. So one -- one -- so the fact that they're going to be sacrificed leads you to

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believe that they're not being treated, correct?

I mean, that's one opinion you have?

A. I think that's an important component.

Q. Okay. And then anything else? Any other relevance to the fact that these are -- animals are going to be sacrificed? How does that affect any of your other opinions about the composition in Boschelli?

A. Well, again, my conclusions are based on my analysis as a whole, and that's really the entirety of the substance of my report. So it's all -- it's all part of analysis of the full disclosure in Boschelli.

Q. Okay.

A. So that full disclosure including the fact that they were not going to survive, they were going to be sacrificed, leads me to the conclusion that I had.

Q. Would that lead a person of ordinary skill in the art, the fact that they were going to be sacrificed, to believe the excipients used were not pharmaceutical grade excipients?

A. Again, I'm -- I'm saying that that is another indication. There's no disclosure that

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they are. And if you look at the totality of the context of the experiments, including the fact that they were to be sacrificed, and that's an important element, but that's -- that is one element of a set of disclosures which leads to my opinion that there's -- and conclusion that there's no indication that these are pharmaceutically acceptable excipients.

Q. Okay. Now, you don't disagree with me that pharmaceutical grade TWEEN 80 is readily available and would have been at the time of the invention, correct?

A. Well, available, it depends what you mean by "ready." One --

Q. It can be purchased?

A. -- it could have been -- could have obtained it. I'm not sure if there would have been delays or what the supply chain would be, but it was obtainable.

Q. Yeah. You could have bought it from Sigma, right, pharmaceutical grade TWEEN 80?

A. Yes, I think that's one possibility.

Q. Okay.

A. Assuming it was in stock.

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Q. And one could have also purchased pharmaceutical grade dextrose from Sigma at the time as well, correct?

A. Yes, I think that's correct.

Q. And one could have easily obtained purified water, correct?

A. Well, again, water, as I've talked, it's not just a matter of purified. It has to be purified and meet certain criteria to be acceptable in a pharmaceutical composition.

Q. But don't laboratories typically -- laboratories that are dealing with pharmaceutical compositions, don't they typically have water purification devices in the laboratories that essentially filter water to create sterile, pure water?

A. Well, I think that's the intention behind, you know, a typical water, let's say, filtration device. I have one in my lab. But I have not specifically analyzed or even used it, tested it to see if it meets some set of standards that would make it pharmaceutically acceptable.

Q. Do laboratories buy pharmaceutically

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acceptable water from Sigma, for example?

A. I'm not sure if Sigma is a supplier, but there are suppliers that one could buy it from.

Q. In your experience do labs buy pharmaceutical grade water, or do they create it in their lab using their own filtration devices?

A. I'm not sure how they -- there are various routes of obtaining it. I'm not sure what's most prevalent.

Q. Okay. And the filtration device you have in your lab, explain to me what -- what is the purpose of that specific device?

A. The purpose is to filter and treat water. My lab is in Cambridge, Massachusetts. They have a certain degree, certain criteria for water. We filter it to try to remove impurities that we don't want in the water that, you know, the City of Cambridge, whoever produces their water, leaves in it.

Q. Would a person of ordinary skill in the art have expected the composition in Boschelli was comprised of water that had been filtered in the same way that you filter water

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in your lab?

A. I'm not sure. There's no indication that it was -- how it was obtained.

Q. But the question is, would a person of ordinary skill in the art reading Boschelli have that expectation, that that's the type of water filtration -- that's the type of water that would have been used in the composition?

A. I think it's possible, maybe likely, but not certain. I mean, I think it would have to be disclosed for someone to be certain about that.

Q. Okay. So there's no absolute certainty that that is what was used in the composition of Boschelli, right?

A. Well, I didn't say absolute certainty. I mean, what is absolutely certain? I -- I said certainty.

Q. Okay.

A. I said it's possible, but it's also possible not.

Q. How about the -- from the perspective of a person of ordinary skill in the art reading Boschelli, would their expectation have been

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that the TWEEN 80 was pharmaceutical grade? TWEEN 80?

A. I think I address this, for example, in my paragraph 74 in which I say, specifically referring to the previous sentence, "Nothing in Boschelli 2001 suggests that the inactive components," including TWEEN 80 in your question, dot dot dot, "in the formulation administered to the laboratory mice were pharmaceutical grade or would have been pharmaceutically acceptable as used." And there's some references.

Q. Okay. I appreciate that. My question was different. Which is, namely, a person of ordinary skill in the art reading -- well, before we get to there, let's agree on one thing.

We can both agree Boschelli is silent as to whether the TWEEN 80 or -- well, let's start with TWEEN 80, is silent as to whether the TWEEN 80 used in the composition of Boschelli was pharmaceutical grade or non-pharmaceutical grade, correct?

MS. PIPER: Objection to form.

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2 A. Correct in the sense there's no  
3 specific disclosure of the source or the grade  
4 of TWEEN 80.

5 Q. Okay. And Boschelli is similarly  
6 silent as to whether the dextrose used in the  
7 compositions of Boschelli was pharmaceutical  
8 grade versus non-pharmaceutical grade, correct?

9 A. That's correct in the sense that  
10 there's no specific disclosure as to the source  
11 or the -- or the type of dextrose.

12 Q. Okay. So with that understanding, my  
13 question is a little bit different then. It is,  
14 a person of ordinary skill in the art reading  
15 Boschelli, what would their expectation have  
16 been based on their own knowledge and experience  
17 as to whether or not the TWEEN 80 was  
18 pharmaceutical grade?

19 A. Yes and -- maybe I don't understand,  
20 if -- to the extent I understand your question,  
21 and I emphasize maybe this helps, all the  
22 opinions in my report are based on the point of  
23 view of a person of ordinary skill in the art as  
24 I've defined it, or -- you know, there's two  
25 different definitions. Either one the opinions

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2 don't change.

3 And that's why I wanted to stick to  
4 specifically what I wrote here in the text  
5 suggests that the inactive components, including  
6 TWEEN 80 -- there's nothing that suggests that  
7 they were pharmaceutical grade or would have  
8 been pharmaceutically acceptable as used;  
9 definitely from the point of view of the person  
10 of ordinary skill in the art.

11 Q. Well, is there anything about a person  
12 of ordinary skill in the art's just experience  
13 that would have led them to believe that the  
14 pharmaceutical excipients used in Boschelli  
15 were, in fact, pharmaceutical grade excipients?

16 MS. PIPER: Objection to form.

17 A. I -- I think -- if you mean some  
18 degree of certainty, I think -- I mean, I would  
19 stick to the words the way I used it in my  
20 report, because I know this is a key question in  
21 the case, but there's no indication that these  
22 are pharmaceutically acceptable or  
23 pharmaceutical grade, and so I don't think the  
24 skilled person would have had certainty that  
25 they are pharmaceutical grade if -- if there's

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2 no indication.

3 And, again, it's also based on the  
4 type of study and the context, and sort of the  
5 overall disclosure in the document, too.

6 Q. Including the fact that the animals  
7 were to be sacrificed, right?

8 A. Yes, that's part of it, including  
9 the -- but also the general context of the study  
10 which is really in the phases of drug discovery.

11 Q. The -- well, would a person of  
12 ordinary skill in the art reading Boschelli  
13 believe it was more likely than not that the  
14 TWEEN 80 used was pharmaceutical grade?

15 MS. PIPER: Objection to form.

16 A. And just to be clear, this sounds to  
17 me like a legal term. Are you asking more  
18 likely than not as --

19 Q. No, it's not.

20 A. Not. Okay. So not a legal term.

21 I think my opinion is that the skilled  
22 person would understand that there's no  
23 indication. I'm not sure what the likelihood  
24 would be in a percentage or even qualitative  
25 way. I would stick to the terms that I used in

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2 my report.

3 Q. So if a person of ordinary skill in  
4 the art was experienced in doing animal studies  
5 and based on that experience understood that  
6 pharmaceutical grade excipients should be used,  
7 how would that -- wouldn't that influence their  
8 expectation about whether the TWEEN 80, for  
9 example, used in the composition of Boschelli  
10 was pharmaceutical grade?

11 MS. PIPER: Objection to form.

12 A. Well, I -- I think I put that -- I  
13 took into account that possibility in -- in my  
14 analysis, and included a lot of, you know,  
15 references and a lot of analyses to achieve  
16 my -- or to, you know, come up with my opinions,  
17 obtain my opinions.

18 MR. BENSON: Let me mark something  
19 here. Could we mark this as Trout  
20 Deposition Exhibit Number 3.

21 (Guide for the Care and Use of  
22 Laboratory Animals was marked Trout Exhibit  
23 3 for identification, as of this date.)

24 THE WITNESS: Thank you.

25 Q. Now, so I've handed you a document we

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2 have marked as Trout Exhibit Number 3, and it is  
3 the Guide for the Care and Use of Laboratory  
4 Animals. Are you familiar with this document?

5 A. No. I'm familiar with the concept but  
6 not this particular document.

7 Q. And when you say you're "familiar with  
8 the concept," what do you mean by that?

9 A. Well, that such guides exist, we  
10 talked about that earlier this morning, and the  
11 various criteria.

12 Q. Okay. All right. So I would like to  
13 direct you to page -- looks like my page numbers  
14 are behind the clip here. Let me see. I  
15 believe it is page 32 of the document. Do you  
16 see the page numbers are at the corner?

17 A. I see the pages.

18 Q. Okay. It's actually page 31 of the  
19 document.

20 Okay. So are you at page 31?

21 A. Yes.

22 Q. Okay. So let's go to that section,  
23 it's italicized, and it is -- it is titled Use  
24 of Non-pharmaceutical Grade Chemicals and Other  
25 Substances. Okay. Now, take a moment to just

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2 read that paragraph there on page 31, and let me  
3 know when you're done.

4 (Witness reviewing document.)

5 A. Okay. I've read this.

6 Q. Okay. Now, according to this document  
7 it states that, "The use of pharmaceutical grade  
8 chemicals and other substances ensures that  
9 toxic or unwanted side effects are not  
10 introduced into studies conducted with  
11 experimental animals."

12 Do you agree with that statement?

13 A. Counsel, that's what's written there  
14 and you read that, I think, accurately. I  
15 haven't seen this document before. It's over a  
16 hundred pages. It's got -- I don't know how  
17 many references, maybe a hundred references or  
18 so. So I would have to analyze this whole  
19 document to opine on a -- a specific statement  
20 as such.

21 I don't even know the -- the chapter,  
22 heading, or other statements in the document.  
23 So I -- I can't sitting here, just now having  
24 read that one paragraph --

25 Q. Sure. We can --

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2 A. -- come up with a conclusion on that  
3 sentence.

4 Q. I'm sorry. I didn't mean to talk over  
5 you.

6 We can agree that the use of  
7 non-pharmaceutical grade chemicals and other  
8 substances -- that's exactly what we've been  
9 talking about for the last 35, 40 minutes,  
10 right?

11 A. Well, I think what we've been talking  
12 about is whether the disclosure in Boschelli  
13 2001 is such that the skilled person would  
14 understand are pharmaceutical grade, and so I  
15 have opined it's not indicated and so it's  
16 uncertain. And so I think that's what we have  
17 been talking about.

18 Q. I get that it's uncertain, and I  
19 understand that. What I've been trying to get  
20 to is what would -- notwithstanding that it is  
21 not disclosed in Boschelli, what would a person  
22 of ordinary skill in the art have expected. And  
23 wouldn't you agree based on -- that this  
24 particular document on page 31, that -- the  
25 paragraph you just read, that the recommendation

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2 here is that pharmaceutical grade excipients  
3 should be used when available for all  
4 animal-related procedures, right?

5 MS. PIPER: Objection to form. And  
6 plaintiffs object to the use of the  
7 document not considered by Dr. Trout in his  
8 report.

9 A. I see that's what's written in the  
10 second sentence in that paragraph.

11 Q. Yeah. It's written that  
12 pharmaceutical grade excipients when available  
13 should be used, right?

14 A. Well, I think it's important to -- you  
15 read the whole sentence accurately before. I  
16 think it's important to take the whole sentence  
17 into account, including the unwanted side  
18 effects, and -- and other aspects. And so the  
19 foc -- and then that's what the "they" refers  
20 to, correct, the pharmaceutical grade chemicals  
21 and other substances.

22 Q. Right. And then there's a citation  
23 here to USDA 1997b. Do you have any  
24 understanding as to what that reference is to?

25 (Witness reviewing document.)

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MS. PIPER: Again, objection.

Dr. Trout has not considered this document in forming his opinion and is not familiar with the document.

A. I'm trying to look up the reference, but it looks like in the back there are all kinds of different sections, and it's not readily evident where that reference is. But I don't --

Q. Okay.

A. -- I don't think it's part of my materials considered.

Q. Okay. Fair enough.

A. Unless I -- unless I'm missing it. We could check the list.

Q. Okay.

A. I don't --

Q. All right. So the next sentence here says, "The use of non-pharmaceutical grade chemicals or substances should be described and justified in the animal use protocol and be approved by the IACUC."

And the citation here is to Wolff, which is the same article you rely upon in your

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expert report, correct?

A. And just to clarify -- I'll answer that and to clarify the previous answer, I did find now that -- it's actually -- the references I think are at the end of the chapter, and maybe located in a different place in the end of the whole document, but -- so I see now the Wolff reference there.

(Witness reviewing document.)

A. And, yes, this looks to be the same reference that is my Exhibit T.

Q. And then the USDA 1997b reference is also indicated there, correct?

A. Yes. I see that now in the -- in the list of references at the end of the chapter, whatever, or section, whatever it is.

Q. And that reference is to the APHIS Policy Number 3, quote, Veterinary Care, July 17. Do you see that?

A. Yes, I see that.

Q. Do you know what APHIS stands for?

A. No. But it's probably written in this document somewhere.

Q. Okay. All right. And based on the

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date of this, do you understand that this would have been the -- the recommendation that they're referring to here that pharmaceutical grade chemicals or substances should be used when available is a policy that had been promulgated at least as early as 1997?

MS. PIPER: Objection to form.

A. I have not reviewed that -- the reference, the USDA 1997b reference, so I'm not sure if this is an accurate characterization. And I haven't reviewed this document either, except for that one paragraph, so I don't know.

Q. Okay. All right. So this document, though, does -- it does cite the Wolff reference that you've relied upon in your -- in your expert report, correct?

A. Yes.

Q. And what it says about Wolff is that the use of non-pharmaceutical grade chemicals or substances should be described and justified in the animal use protocol and be approved by AUCUC, right?

A. IACUC, yes.

Q. I apologize.

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A. IACUC. Yes. That's what's written here.

Q. So wouldn't a person of ordinary skill in the art expect that if -- that if non-pharmaceutical grade chemicals were used, that that would be disclosed in the study protocol?

MS. PIPER: Objection to form.

A. Again, I'm looking at one sentence and one paragraph, and that's all I've read in this hundred-page document with lots and lots of references. But I'm -- I'm not -- I don't think that Boschelli is disclosing a protocol per se. Part of a protocol or maybe that is the disclosure of the protocol. But I'm not, frankly, sure exactly what this sentence refers to, so I would really have to study this whole document in detail.

Q. But wouldn't you agree with me that based on the information in this document, a person of ordinary skill in the art would first expect that pharmaceutical grade excipients would be used in animal studies when those excipients are available?



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 2 MS. PIPER: Objection. Dr. Trout has  
 3 not had a chance no review this document  
 4 and has not considered it in forming his  
 5 opinion.

6 A. I'm not sure if that's what the  
 7 document concludes or even indicates,  
 8 particularly in the context of the Boschelli  
 9 2001 article.

10 Q. Okay. Well, wouldn't a person of  
 11 ordinary skill in the art have understood that  
 12 if non-pharmaceutical grade chemicals or  
 13 substances were used, that that should be  
 14 disclosed in the study protocol?

15 MS. PIPER: Objection. Dr. Trout has  
 16 not had a chance to review this document  
 17 and has not considered it in forming his  
 18 opinion.

19 A. I mean, again, I read the sentence as  
 20 such. I'm not sure of the broader context. And  
 21 I think one would have to understand the -- the  
 22 document as a whole to interpret what a given  
 23 sentence and given paragraph and given chapter  
 24 means.

25 Q. Well, the context as a whole is Wolff,

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 2 right? Because that's what Wolff says, right?

3 A. No --

4 Q. If we go back to Wolff, it says:  
 5 Specific review and approval by IACUC has to  
 6 be -- has to be achieved for the use of  
 7 non-pharmaceutical grade excipients.

8 Right?

9 MS. PIPER: Objection to form. And  
 10 Dr. Trout has not had a chance to review  
 11 this document.

12 MR. BENSON: I just read from Wolff,  
 13 and he reviewed it and discussed it at  
 14 length.

15 Q. Isn't it true that Wolff explicitly  
 16 states that, when using non-pharmaceutical grade  
 17 excipients, specific review and approval by the  
 18 IACUC must be obtained?

19 A. Well, going back to Wolff, I mean,  
 20 that's one of three possibilities in -- in this  
 21 list from Query 3 in the middle column on  
 22 page 34. He discussed that there are other  
 23 possibilities. And, again, these -- these are  
 24 under a broader statement in Wolff.

25 Q. Now, the very last -- one of the

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 2 sentences in Wolff that, you know -- in that  
 3 first question, the second part of that that you  
 4 noted was, it states: Please clarify whether  
 5 this -- and "this" is the use of  
 6 non-pharmaceutical grade excipients -- is an  
 7 allowable practice and whether it makes a  
 8 difference if the compounds are used in survival  
 9 versus non-survival experiments.

10 Right?

11 A. Yes, that's what's written there.

12 Q. What does Wolff say about that?

13 Well, let me ask a different question.  
 14 Isn't it true that Wolff says that  
 15 notwithstanding the use of non-pharmaceutical --  
 16 of pharmaceutical grade excipients -- let me  
 17 rephrase that.

18 Isn't it true that Wolff states that  
 19 it doesn't matter whether the studies are  
 20 non-survival studies, the scientific principles  
 21 requiring the use of pharmaceutical grade  
 22 excipients is -- still remain the same?

23 A. You know, I think you're referring to  
 24 the next to the last sentence in the bottom. It  
 25 doesn't quite say it the way you stated. It

1 Trout - Confidential  
 2 really says, "Although the potential animal  
 3 welfare consequences of complications are less  
 4 evident in non-survival studies, the scientific  
 5 issues remain the same."

6 That's what he says.

7 Q. Right. And the scientific issue is  
 8 that, all things being equal, if the  
 9 pharmaceutical grade excipients is available,  
 10 that's what should be used. Isn't that what  
 11 Wolff is saying?

12 MS. PIPER: Objection to form.

13 A. I don't think Wolff says that.

14 Q. Well, it says, Under certain  
 15 circumstances one could use non-pharmaceutical  
 16 grade excipients. Isn't it true that a person  
 17 of ordinary skill in the art reading that would  
 18 say, generally you have to use pharmaceutical  
 19 grade excipients, under these circumstances  
 20 outlined here it may be justifiable to use  
 21 non-pharmaceutical grade excipients?

22 A. Well, that's correct. But the -- the  
 23 circumstances of Boschelli, because -- Boschelli  
 24 2001 are different, let's say, than other  
 25 circumstances.

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Q. In what way?

A. So -- okay. Just to clarify, and then I'll segue to your question. So Wolff is talking about a variety of different circumstances. And -- and so -- and getting to your question, the circumstances around Boschelli are that the animal experiments are done on mice, and they're done early on in the discovery, as opposed to animal experiments that are done later, like, under preclinical context. And so -- so I think one has to take into account those circumstances in understanding the answer here in Query 3 in Wolff.

Q. What's the justification for using non-pharmaceutical grade excipients when you're administering something to a living animal?

Let me ask a different question. Don't researchers working with laboratory animals have a duty to ensure that the research they're doing causes the least possible harm to the animal?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I'm not sure if they have that duty or

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not. I don't have an opinion on that.

Q. I mean, isn't that what the, you know, Guideline for the Use and Care of Animals is all about is protecting animals used in laboratory research?

MS. PIPER: Objection. Again, Dr. Trout has not had a chance to review the entire Guideline for the Care and Use of Laboratory Animals.

Q. You can answer the question.

A. I -- I don't know. I'm not sure -- I haven't read the whole -- and studied this whole document.

Q. Research laboratories are required to have a veterinarian on staff, right?

MS. PIPER: Objection. Outside the scope of the Dr. Trout's opinion.

A. I mean, I'm not sure what you mean. Not all research laboratories. Maybe some.

Q. Do you have any understanding as to what are the requirements for providing veterinary care to laboratory animals?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

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A. I don't have an opinion on that.

Q. Would it change your -- you testified earlier today that the pharmaceutical compositions of the '625 patent are compositions that are appropriate for human or veterinary use, right?

A. In Claim 1 of the '625, yes, it's my understanding.

Q. And if -- if laboratory animals are under the care of veterinarians who are overseeing the medicines being administered to animals, isn't that veterinary care?

MS. PIPER: Objection to form. And objection. Outside the scope of Dr. Trout's opinion.

A. I don't have an opinion on that matter.

Q. Okay. Would it change your opinion if the animals in this particular study were -- were under the care of a veterinarian and the procedures were being overseen by a veterinarian?

A. I mean, I would have to -- I would take that into account. There's no disclosure

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in Boschelli as such. So I'm not sure, sitting here, how that hypothetical would change my opinions or not.

Q. Okay. You don't disagree the intent of administering the composition of Boschelli was to inhibit tumor growth in the laboratory mice, right?

MS. PIPER: Objection. Outside the form -- scratch that. Objection. Outside the scope of Dr. Trout's opinion.

A. I don't think I opined upon the intention as such.

Q. You said that the animals weren't being treated; is that right?

A. I believe that's what I said. I may have said more and qualified that. But I think what I said is they're not -- stick maybe to what -- my original answer, but they're not intended to be treated to cure disease. They're intended to test different hypotheses, and -- and in the end to be sacrificed.

Q. How does that matter to an anticipation argument on a claim that doesn't require or include a limitation that is a method

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2 of treating --  
3 MS. PIPER: Objection to form. And --  
4 Q. -- an animal?  
5 I mean, the claim doesn't say -- let  
6 me -- you know, let me ask it in a different  
7 way, and namely first by directing you to the  
8 claim at issue. You can go back to -- I believe  
9 it was at paragraph 40 --  
10 A. 42.  
11 Q. 42. Thank you.  
12 The claim itself is just, "A  
13 pharmaceutical composition comprising a CML  
14 inhibiting amount of bosutinib."  
15 Right?  
16 MS. PIPER: Objection to form.  
17 A. I think that's what it says, yes,  
18 pharmaceutical composition --  
19 Q. So the only issue is, is the  
20 composition in Boschelli a pharmaceutical  
21 composition, right?  
22 MS. PIPER: Objection to form.  
23 Q. That's one issue, correct?  
24 A. Yes, that's the -- the major issue  
25 that I opined upon.

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2 an opinion as to whether or not the bosutinib in  
3 the Boschelli composition is a CML inhibiting  
4 amount of bosutinib, correct?  
5 A. That's correct. I do not have -- did  
6 not express opinions about CML inhibiting  
7 amounts.  
8 Q. Okay. All right. Now, so given your  
9 opinion as focused solely on the pharmaceutical  
10 composition, I do want to return to paragraph  
11 29, which includes the Court's construction.  
12 And I just want to recapitulate where we are in  
13 agreement on pharmaceutical composition,  
14 specifically looking with reference to the  
15 Court's construction. Okay?  
16 MS. PIPER: Objection to form.  
17 MR. BENSON: That wasn't a question.  
18 Q. Okay. So the Court's construction --  
19 MR. BENSON: I'll give you a minute.  
20 MS. PIPER: Sorry.  
21 MR. BENSON: That's quite all right.  
22 Those are unwieldy binders.  
23 MS. PIPER: Okay. Thanks.  
24 MR. BENSON: You're welcome.  
25 Q. Okay. So, again, the Court's

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2 Q. And the second issue, is the amount of  
3 bosutinib a CML inhibiting amount?  
4 MS. PIPER: Objection. Outside the  
5 scope of Dr. Trout's opinion.  
6 Q. Right?  
7 A. That's part of the claim, and I didn't  
8 opine upon the CML inhibiting amount.  
9 Q. Okay. So your entire opinion is based  
10 solely on whether it's a pharmaceutical  
11 composition, correct?  
12 A. It being the -- what's disclosed in  
13 the Boschelli 2001. That was the focus of my  
14 opinions.  
15 Q. Okay. So I'll ask that again in a  
16 better way, and you're right. So your opinion  
17 is focused solely on whether or not the  
18 composition of Boschelli is a pharmaceutical  
19 composition as that term has been construed by  
20 the Court in this case, correct?  
21 A. Well, that's correct in specifically  
22 responding to Dr. -- some of Dr. Lindsley's  
23 opinions in that regard, but that's the focus of  
24 my report, though.  
25 Q. And just for clarity, you do not give

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2 construction is, "A pharmaceutically acceptable  
3 composition containing the specified compound,"  
4 in this case bosutinib, "and one or more  
5 excipients."  
6 Right?  
7 A. Yes.  
8 Q. Okay. We agree the composition of  
9 Boschelli includes -- contains bosutinib, which  
10 is under the Court's construction the specified  
11 compound, right?  
12 MS. PIPER: Objection to form.  
13 A. Well, I think -- if you're talking  
14 about a -- a chemical structure per se, which is  
15 somewhat abstract, that's there. But, again,  
16 that's a -- whether it's an API and the -- the  
17 way it was made in Boschelli 2001 and the way it  
18 was characterized, those are central aspects to  
19 my opinions in this case.  
20 Q. Okay. I'll ask it again. I think my  
21 question was a little bit cleaner. Namely, the  
22 composition of Boschelli contained bosutinib,  
23 right?  
24 A. Again, I -- it would just stick to my  
25 answer. I think it's the same question, which

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2 is that if you're just talking abstractly about  
3 the molecule, the chemical formula, that's what  
4 is characterized as 31a in Boschelli 2001.

5 But if you're talking about impurity  
6 profiles, acceptability as an API, and those  
7 aspects, which I think are important aspects  
8 of -- of what goes into a composition, then I  
9 express a large number of opinions about that.

10 Q. I understand, but that's not my  
11 question. My question is very simple. It's a  
12 yes or no. Does the composition of Boschelli  
13 contain bosutinib?

14 A. And in your -- just to clarify in your  
15 yes-or-no question, by "bosutinib," you mean  
16 abstractly this chemical formula, which is an  
17 abstraction of what a -- a chemical is, or do  
18 you mean bosutinib as would go into a  
19 pharmaceutical composition, or something else?

20 Q. I don't think -- I don't think the  
21 chemical formula of bosutinib is an abstract in  
22 any way, shape, or form, is it?

23 MS. PIPER: Objection to form.

24 Q. I mean, that confuses me.

25 A. In my view as a chemist, a chemical

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2 formula is an abstraction of what's there. It's  
3 maybe a model or an indication.

4 Q. It's a precise definition of what the  
5 chemical entity is, right?

6 I mean, that's how you know what it  
7 is. A chemist can read a chemical formula and  
8 know exactly what it is, right?

9 MS. PIPER: Objection.

10 Q. It knows how many carbons, how many  
11 nitrogens, how many hydrogens, how many oxygens,  
12 right?

13 A. Yes, it allows you to count those.

14 Q. Yeah, and the way that the -- the way  
15 that the chemical formula is constructed, it  
16 also gives the chemist information as to how  
17 those various atoms are connected to one  
18 another, right?

19 A. That's what a two-dimensional chemical  
20 representation does, yes.

21 Q. Okay. So the question is -- and we've  
22 already agreed that that chemical formula in  
23 Claim 1 is bosutinib, right?

24 A. Bosutinib the molecule, yes.

25 Q. That's right. That's what's stated

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2 there. And that's what the claim is all about,  
3 does it have that molecule? That's the  
4 compound, right?

5 MS. PIPER: Objection to form.

6 Q. That's what the claim is about, it's  
7 about the compound bosutinib?

8 A. It's not all about that, Counselor,  
9 no. It's about other -- there are other  
10 elements, too.

11 Q. Well, let's go back to the claim. The  
12 claim says, "A pharmaceutical composition  
13 comprising a CML inhibiting amount of the  
14 compound," and then it names the chemical  
15 formula which is bosutinib, right?

16 A. Right, as the chemical.

17 Q. That's the chemical, right. That's  
18 what I'm asking. That's bosutinib. That's what  
19 the claim is all about. It's not about an  
20 abstraction. It's not about whether or not it  
21 was pure or how it -- whether the column  
22 chromatography was done, you know, properly  
23 or -- it doesn't matter. The question I have  
24 is, does the composition of Boschelli contain  
25 bosutinib?

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2 MS. PIPER: Objection to form.

3 A. Well, in -- qualify in my opinion in  
4 reading this as a chemist, there -- there are  
5 other parts like pharmaceutical composition.  
6 But --

7 Q. I'm not asking about those. I just  
8 want a yes or no. Does the composition of  
9 Boschelli contain bosutinib? Yes or no?

10 A. It contains that molecule --

11 Q. Thank you.

12 A. -- 31a, as I've testified to. 31a.

13 Q. Which is bosutinib, correct?

14 MS. PIPER: Objection to form.

15 A. It's the bosutinib chemical, if we  
16 talk about it, that -- if that's the focus of  
17 it, it's -- but --

18 Q. Let me do it a different way.

19 A. Just to finish my answer, Counselor,  
20 please.

21 Q. You know what? I -- I withdraw the  
22 question. Let me ask a different question.

23 Does the formulation, or -- strike  
24 that.

25 Does the composition of Boschelli

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 contain 4-[(2,4-dichloro-5-methoxyphenyl) amino]  
 -6-methoxy-7-[-3-(4-methyl-1-pyrazinyl)propoxy  
 ]-3-quinolinecarbonitrile? Yes or no?

A. Again, I'm not sure if you got all the  
 brackets right, but we know it's written there.  
 So what I'm trying to say is that the -- this  
 particular compound as such is -- is part of  
 what's in Boschelli Reference Number 31a.

Q. So, yes, the composition of Boschelli  
 includes bosutinib, right?

A. If that's what we're defining  
 bosutinib is, is that chemical formula.

Q. Okay. Can you assume in the question  
 I asked that when I say "bosutinib," I mean the  
 chemical formula? I'm sorry. I thought that  
 was clear. When I say "bosutinib," I mean that  
 chemical formula. Okay? That's what I mean.

MS. PIPER: Objection to form.

Q. Do you understand?

A. Yes.

Q. Okay. Does the composition of  
 Boschelli contain bosutinib?

A. Again, under your definition, this  
 chemical formula, yes.

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Q. Okay. And does the composition of  
 Boschelli contain one or more excipients? Yes  
 or no?

A. So, for example -- on page 15 of my  
 report, 53, I talk about excipients as  
 ingredients of a pharmaceutical composition  
 other than the active ingredient. From that  
 standpoint since Boschelli does not contain  
 or -- is likely not to contain pharmaceutical  
 compositions, and all the -- I mean, this is  
 really the whole focus of my report, I would not  
 call those excipients.

Q. Okay. So it is your opinion that the  
 composition of Boschelli does not include any  
 excipients, right?

A. Well, again, there's no indication  
 that what's included are pharmaceutically  
 acceptable. Certainly TWEEN, dextrose, and  
 water can be excipients, and they're in the  
 Handbook of Pharmaceutical Excipients. And  
 they're likely on the GRAS list, as we discussed  
 earlier.

But if we're defining as I do here  
 that they have to be in a pharmaceutical

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 composition for -- and this is just a summary  
 statement for all the reasons which I discuss  
 here, then they're not excipients as such  
 because it's not likely to be a pharmaceutical  
 composition.

Maybe if someone were to go back and  
 characterize it, and -- maybe they actually do  
 meet specs but there's no indication that they  
 do, and so there's no indication that they're a  
 pharmaceutical composition, or that they're  
 excipients that are ingredients of a  
 pharmaceutical composition.

Q. Okay. One second.

THE COURT REPORTER: Counsel, when you  
 get to a good moment, I could use a break.

MR. BENSON: Yeah. That's what I was  
 getting at. Let's take a break.

THE VIDEOGRAPHER: The time is  
 11:59 a.m., and we are going off the  
 record.

(Luncheon recess at 11:59.)

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AFTERNOON SESSION  
 (1:00)

BERNHARDT TROUT, Ph.D.

resumed, having been previously duly  
 sworn by a Notary Public, was  
 examined and testified further  
 as follows:

THE VIDEOGRAPHER: The time is 1:00,  
 and we are back on the record.

CONTINUED EXAMINATION BY MR. BENSON:

Q. Welcome back, Dr. Trout.

A. Thank you.

Q. So returning to the claim language,  
 what -- and I know we talked about this earlier  
 in the context of what the term means generally  
 to a person of ordinary skill in the art. But  
 what does a -- what does the term  
 "pharmaceutical" mean to you in the context of  
 the claim at issue here; namely, Claim 1 of the  
 '625 patent?

A. So -- and I think it's important,  
 Counselor, it's -- pharmaceutical composition go  
 together here, and I use the construction  
 that -- as I elaborate in paragraph 29 of my

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 report that the Court construed. And so  
 pharmaceutical composition is what the Court  
 construed and what's written there, "A  
 pharmaceutically acceptable composition  
 containing the specified compound and one or  
 more excipients.

Q. Well, pharmaceutical is an -- it's an  
 adjective, right? And it's modifying  
 composition?

MS. PIPER: Objection to form.

A. Yes. And I guess it's an adverb as  
 used by the Court's construction.

Q. Okay. So in the context of its use in  
 the claim, just pharmaceutical, I mean, what is  
 your understanding of that -- the adjective?  
 What does it mean?

I mean, adjectives in their own right  
 have meaning, right?

MS. PIPER: Objection to form.

A. Well, I think pharmaceutical  
 composition go together, and my understanding is  
 that that's, you know, a part of a -- a claim.  
 And so if you're asking me about the specific  
 use in this claim, I think it has to go

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 together.

And I can opine on -- or I can tell  
 you, you know, broadly outside of the context of  
 this claim pharmaceutical by itself. But  
 with -- within the claim, I think it has to go  
 with composition.

Q. Well, but each word has its own  
 meaning, right? I mean, the -- an adjective  
 pharmaceutical has a meaning separate and apart  
 from the noun composition; isn't that correct?

MS. PIPER: Object to form. Objection  
 to form.

A. I mean, obviously to the extent that  
 you're asking me a legal conclusion, I leave  
 that to the lawyers to decide. My understanding  
 is that the way the Court looks at it, they go  
 together. If you mean just broadly  
 grammatically, that's correct, they're two  
 separate words.

Q. And so what does pharmaceutical, the  
 adjective, mean to you? Again, just in your --  
 in the context of understanding this particular  
 patent, what does that term mean to you  
 "pharmaceutical"?

Trout - Confidential  
 A. Again, you mean -- by "the context"  
 you mean not what's the word in the claim term  
 but just broadly within the context of the  
 patent? Or --

Q. Right. Based on your reading of the  
 patent, what is your understanding of what  
 pharmaceutical means?

A. Okay. So if -- in the context of the  
 patent, I think it's an adjective that modifies  
 composition. So composition is, you know,  
 some -- let's say, as the Court construes, some  
 mixture of different compounds, and the  
 specifics are there.

And then the pharmaceutical modifying  
 composition means that it's not just any  
 composition. It has to be a pharmaceutical  
 composition. And I discuss -- I mean, really,  
 my whole report is about that one term, and so  
 it's all -- all my opinions relate to, really,  
 that term.

Q. So we can agree that from the Court's  
 construction, composition is just generally  
 the -- a composition that contains the necessary  
 components articulated in the construction

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 itself, namely bosutinib and one or more  
 excipients, right?

MS. PIPER: Objection to form.

A. Right. I guess the specified compound  
 and one or more excipients in the specified  
 compound is -- is, you know, a chemical term,  
 which we've been discussing, which -- you know,  
 depends on how you want to define it. It's a --  
 a molecular formula which is related to the, you  
 know, active bosutinib, but abstracted from the  
 actual situation in which it's in, in which  
 there were impurities and there are other  
 aspects to it.

Q. Right. So -- but the -- what I'm  
 getting at is that we -- we have an  
 understanding, or I have an understanding as to  
 what you're -- what you understand composition  
 to mean in the context of the Court's  
 construction; namely, it's a composition  
 containing bosutinib and one or more excipients,  
 right?

So -- correct?

A. Well, again, we have been -- we were  
 discussing this morning what bosutinib means,

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2 and we have to be clear from the context. I  
3 mean, there's --

4 Q. With all due respect, if I have not  
5 been clear that when I say "bosutinib," I mean  
6 the chemical structure, the compound bosutinib,  
7 I apologize, but that's what I mean. I don't  
8 mean anything else. If I'm talking about  
9 anything other than that, I will let you know.  
10 But there is -- here it's a compound. I mean,  
11 in the chemical arts, what does a compound mean?

12 A. In the chemical arts, and I know it  
13 can be used differently in -- maybe legal or  
14 otherwise, but specifically in chemistry, a  
15 compound is a -- let's say a defined set of  
16 atoms which are connected through chemical  
17 bonds.

18 Q. Okay. And that is exactly the way I'm  
19 using bosutinib here because the composition --  
20 the elements of the composition pursuant to the  
21 Court's construction is, it contains a specified  
22 compound, which is bosutinib, the compound, as  
23 that is used in -- in chemistry and one or more  
24 excipients, right?

25 A. Okay.

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2 Q. Okay. So we're in agreement on that,  
3 right? A composition is a -- according to the  
4 claim is a composition -- now, again, I  
5 understand your opinion about pharmaceutically  
6 acceptable, and we'll get to that. But just for  
7 clarity, a composition is a composition that  
8 contains bosutinib and one or more excipients,  
9 right?

10 A. Again, right, if you're defining  
11 bosutinib as this chemical formula. It's --

12 Q. But what --

13 A. Sorry. Can I just finish my sentence?  
14 Thank you.

15 Q. Yes.

16 A. Because -- I mean, that -- but that's  
17 a key point of my opinions is that if you're  
18 talking about it as an API, or as a potential  
19 ingredient that could be pharmaceutically  
20 acceptable or not, then it's not just the  
21 specific compound with a -- a specific molecular  
22 formula. It's abstracted from the real  
23 situation of impurity profile and the way it's  
24 manufactured and whatnot.

25 Q. Dr. Trout, I appreciate that you have

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2 opinions and that those -- the opinions relate  
3 to that particular topic, but --

4 MS. PIPER: Objection.

5 Q. -- what I'm looking to is the Court's  
6 construction that said a composition contains  
7 the specified compound, right?

8 And we just went through what is the  
9 compound. The compound here is bosutinib. And  
10 it's a compound. It's not an API. It's not an  
11 aggregate of compounds and a bunch of other  
12 garbage that may or may not be present. It's  
13 the compound. And that's what I'm talking  
14 about, the Court's construction.

15 The Court's construction of the claim  
16 is a composition containing the specified  
17 compound, which is bosutinib, right? The  
18 chemical entity, the compound, bosutinib, and  
19 one or more excipients, right?

20 MS. PIPER: Objection to form.

21 Q. I mean, do you need to look at the  
22 construction? Because it says "specified  
23 compound," and we agree that the specified  
24 compound -- I thought that was one of the very  
25 first things we did today is we talked about the

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2 specified compound being that chemical structure  
3 that is articulated in the claim, and we agreed  
4 that that structure was bosutinib, right?

5 A. Right, in the sense I'm happy to  
6 consider this chemical structure that's in  
7 Claim 1 to be bosutinib just with a -- you know,  
8 make sure that we agree that if we call that  
9 bosutinib, that's that chemical structure per  
10 se, not another manifestation of that in a  
11 particular environment.

12 Q. Right. But it -- correct me if I'm  
13 wrong, but there is the question -- the question  
14 you're getting to is whether or not there is an  
15 inhibiting amount of CML -- a CML inhibiting  
16 amount of the compound, right?

17 MS. PIPER: Objection.

18 Q. It's, like, how much bosutinib is in  
19 there, and what does it look like, right?

20 MS. PIPER: Objection. Outside the  
21 scope of what Dr. Trout opined on.

22 Q. That's exactly right. You didn't  
23 consider that at all, right? You didn't  
24 consider how much bosutinib or -- is -- the  
25 claim requires, right?

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 2 MS. PIPER: Objection. Outside the  
 3 scope of what Dr. Trout opined on.  
 4 A. And I'm confused because there's  
 5 multiple questions --  
 6 Q. You didn't opine on how much bosutinib  
 7 has to be in the composition of the claim,  
 8 right?  
 9 MS. PIPER: Objection to form.  
 10 A. That's correct. I did not opine on a  
 11 specific amount in this claim.  
 12 Q. So then I just want you to focus on  
 13 the compound itself, just bosutinib. Because  
 14 the part of the claim that you did consider and  
 15 opine upon is pharmaceutical composition, and  
 16 that part of the claim, that part which is all  
 17 you've testified -- all your opinion relates to,  
 18 is that -- a pharmaceutically acceptable  
 19 composition containing the specified compound,  
 20 bosutinib, and one or more excipients, right?  
 21 A. Yes, again, that's fine for a --  
 22 defining bosutinib as the -- the chemical  
 23 formula --  
 24 Q. And we are.  
 25 A. -- which is in the claim.

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 2 And I talk about all the reasons why  
 3 there are other things in these -- these  
 4 non-pharmaceutical compositions, potentially  
 5 non-pharmaceutical compositions.  
 6 Q. Right. It is your opinion that  
 7 pharmaceutically acceptable excludes any kind of  
 8 impurities in the composition, right?  
 9 A. No, that's not what -- my opinion.  
 10 Q. Okay. How much -- how many -- what  
 11 level of impurities can one have in a  
 12 pharmaceutical composition?  
 13 A. So my understanding as a technical  
 14 expert is that there's a procedure that one  
 15 would have to go through to determine and make  
 16 the case for what's acceptable in a particular  
 17 situation for a particular, you know, proposed  
 18 active.  
 19 Q. And your opinion relates on the things  
 20 that a person of ordinary skill in the art has  
 21 to do to obtain FDA approval to sell a drug,  
 22 right?  
 23 MS. PIPER: Objection to form.  
 24 A. No, that's -- that's -- I mean, that's  
 25 part of it, but I talk a lot about a lot of

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 2 Q. And we are. So a composition,  
 3 according to the claim -- and then I want to get  
 4 to your opinion which really relates to  
 5 pharmaceutically acceptable, correct?  
 6 MS. PIPER: Objection to form.  
 7 A. My opinion relates to -- I mean,  
 8 everything that I discuss in my report. And  
 9 pharmaceutically acceptable is a major part of  
 10 it, and the specifics of the Boschelli reference  
 11 is also a major part of it.  
 12 Q. Right. We agree that there is a  
 13 composition in Boschelli, right? I mean, we  
 14 agreed about that this morning?  
 15 A. Yes. We can call them a composition.  
 16 There are a variety of compositions.  
 17 Q. Right. And the compositions contain  
 18 bosutinib and one or more excipients, right?  
 19 A. Again, if you are defining -- I mean,  
 20 they contain other things potentially in them.  
 21 Those are the key aspects that we have been  
 22 focusing on, but my report -- I talk about the  
 23 impurity profiles and I talk about all kinds of  
 24 other aspects to -- to what's in there, even  
 25 though they may not be explicitly stated.

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 2 aspects. It's not -- it's not so crystalized as  
 3 such.  
 4 Q. Okay. So a pharmaceutical composition  
 5 does not have to be an FDA approvable  
 6 composition, correct?  
 7 MS. PIPER: Objection to form.  
 8 A. Not necessarily. I think it -- I  
 9 think that -- that certainly if it's FDA  
 10 approvable -- I'm not sure what that means. If  
 11 it -- but if it's FDA approved, let's say,  
 12 then -- then that -- that's certainly one  
 13 example, but that's not the only example.  
 14 Q. Okay. So a pharmaceutical composition  
 15 pursuant to the claims, in your opinion, does  
 16 not have to be a composition that would meet the  
 17 standards of FDA approval for a human drug,  
 18 right?  
 19 MS. PIPER: Objection to form.  
 20 A. Yes, that's correct.  
 21 Q. Okay.  
 22 A. Not necessarily. That's an example of  
 23 what it could be.  
 24 Q. Okay. So does it have to be a  
 25 pharmaceutical composition that would meet the



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2 standards for administering the composition to  
3 an animal, for example?

4 MS. PIPER: Objection to form.

5 A. Again, I think that's another example  
6 of what could be -- again, given my  
7 understanding of the construction of this claim,  
8 that would fall under a pharmaceutically  
9 acceptable composition.

10 Q. Right. But the question is, does it  
11 have to be a composition that would meet the  
12 standards of approval for a composition that  
13 could be administered to an animal?

14 A. I don't -- well, maybe potentially  
15 approvable by -- by someone, but that's not --  
16 it's not like a threshold, or a, you know,  
17 rock-solid criterion.

18 Q. Okay. What if it's a -- what if it's  
19 a composition that the IACUC approves for the  
20 administration to animals in a laboratory  
21 context? Would that meet the standard?

22 A. I'm -- I'm not sure if it would meet  
23 the standard. I would have to -- I would have  
24 to understand the context and -- and what it was  
25 approved to do. And, again, there are different

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2 kinds of animal studies. And -- and we talked  
3 about what Boschelli 2001 is. And so it depends  
4 what it's approved for.

5 Q. What is IACUC? Do you know what that  
6 stands for?

7 A. Yeah, it's -- I don't know off the top  
8 of my head but it's in Wolff -- it's the  
9 Institutional Animal Care and Use Committees --  
10 or Committee, I guess, without the S.

11 Q. So Institutional Animal Care --

12 A. And Use Committee.

13 Q. -- and Use Committees.

14 A. Committees with plural.

15 Q. And what is your understanding of what  
16 the role of the IACUC is in the context of a  
17 research laboratory?

18 MS. PIPER: Objection. Outside the  
19 scope of what Dr. Trout was asked to opine  
20 on.

21 A. I don't have an opinion on that.

22 Q. Do they have to approve protocols for  
23 the administration of compositions to animals?

24 MS. PIPER: Objection. Outside the  
25 scope of what Dr. Trout was asked to opine

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2 on.

3 A. I don't have an opinion on that.

4 Q. Do pharmaceutical companies have  
5 IACUC -- let me ask that a different way.  
6 That's kind of a weird construction.

7 Do pharmaceutical companies have  
8 Institutional Animal Care and Use Committees  
9 within their organizations?

10 MS. PIPER: Objection. Outside the  
11 scope of Dr. Trout's opinion.

12 A. I don't have an opinion on that.

13 Q. Do pharmaceutical companies employ  
14 veterinarians to oversee the care of the animals  
15 they may or may not be using in research?

16 MS. PIPER: Objection. Outside the  
17 scope of Dr. Trout's opinion.

18 A. It's not an opinion that I have.

19 Q. Okay. All right. So if the  
20 composition of -- well, if a composition  
21 intended to be administered to laboratory  
22 animals for the purpose of gauging its  
23 therapeutic potential is approved by the IACUC,  
24 would that composition be a pharmaceutically  
25 acceptable composition pursuant to the claims of

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2 the '625 patent?

3 A. In this hypothetical, I think it  
4 depends on the details and what it was approved  
5 for and the reason behind the approval. I --  
6 it -- the details are important.

7 Q. So you would have to know more  
8 details.

9 What if -- what if the composition of  
10 Boschelli was approved by an Institutional  
11 Animal Care and Use Committee? Would that  
12 change your opinion about whether or not that  
13 composition was a pharmaceutical composition?

14 MS. PIPER: Objection to form.

15 A. If there's additional information  
16 regarding the Boschelli 2001 reference, I would  
17 certainly take that into account. I would have  
18 to analyze that information to determine how  
19 that affects my opinions.

20 Q. Okay. So the -- so if, in fact, there  
21 were evidence that the IACUC had approved of the  
22 composition being administered to the animals in  
23 Boschelli, that could impact your opinion as to  
24 whether or not that formulation in Boschelli was  
25 a pharmaceutical composition, correct?

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MS. PIPER: Objection to form.

A. It may or may not. If there's additional information about Boschelli outside of the reference and the other references which I considered, I would take that into account.

Q. All right. So a pharmaceutical composition as the Court has constructed it, as far as whether it's pharmaceutically acceptable, it doesn't rise to the standard of something that would be approvable by the FDA for human use, right? That's your testimony?

MS. PIPER: Objection to form.

A. I think my testimony as I gave it before is that that could be one example, but there are other potential examples.

Q. Right. But the question is a little bit different. I just want to make sure I'm absolutely clear that it is not your opinion that pharmaceutically acceptable means the composition has to be a composition that would be approvable by FDA for human use, right?

MS. PIPER: Objection to form.

A. I'm not sure what it means that something is approvable. I think what you're

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asking is if it hypothetically had gone through the FDA approval, that's the only thing that I understand. Because -- and in --

Q. Right. A composition could be a -- a composition according to the claims could be a composition that is being used for research purposes, right?

MS. PIPER: Objection to form.

A. Well, it depends on what kind of research. Broadly speaking, in its -- it's possible.

Q. So if it's being administered to humans for the purposes of researching its therapeutic potential, is it a pharmaceutical composition?

A. Again, one would have to go through the same kind of analysis that I went through in, whatever, 25 or so pages on the Boschelli, you know, given the details of this hypothetical you're posing, to make an opinion upon that.

Q. Okay. So based on that response then is it your opinion that it is possible that a composition being administered to patients in a Phase III clinical trial may not be

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pharmaceutically acceptable pursuant to these claims?

MS. PIPER: Objection to form.

A. I mean, look, may, there's always some possibility. I would generally think that a composition that's been approved to go through Phase III trials would be pharmaceutically acceptable. There may be exceptions to that. Again, you're asking a broad hypothetical. But generally, I would expect that that would be pharmaceutically acceptable.

Q. Okay. Pushing that a little bit further, would you assume a composition that has been approved to administer to a human in any clinical context would be pharmaceutically acceptable?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and...

A. Yeah, I didn't give an opinion about clinical broadly, and I'm trying to give examples of what could be pharmaceutically acceptable. Again, the -- the focus on my report was on the Boschelli 2001, and, you know, the analysis that I've done of that reference.

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Q. Can you think of any example where there's a composition administered to humans and it would not be pharmaceutically acceptable?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion and report.

A. I don't have an opinion about that per se.

Q. Do you have any opinion about -- strike that.

Do you have any opinion about what a composition administered to a laboratory animal would have to look like in order for it to be considered pharmaceutically acceptable?

A. Yes. I think it would have to meet some of the criteria, or the -- the bulk of the criteria that I've gone through here in this report, which Boschelli doesn't meet any of those criteria I've talked about. I think it would have to meet some of them. And, again, it would depend on the context, what the study was done for, and I would have to analyze those details.

Q. Why does it matter what the study is being done for, in your opinion?

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A. Because it matters whether the study is attempting to treat animals or is basically doing a study with hypotheses, for example, about how chemicals work, leading to the destruction of those animals one way or another.

Q. What in the Court's construction leads you to believe that pharmaceutically acceptable composition has to be one that is being administered for the purposes of treating?

A. I did not say that it has to be.

Q. Okay.

A. I said that's a potential, you know, example. But that's not really the threshold. I think the threshold is what I've gone through in this report, and it has to, you know, meet some of the criteria. And I've discussed in particular why Boschelli 2001 doesn't meet any of those criteria.

Q. So a pharmaceutically acceptable composition could be a composition that's being administered to an animal even though it's not being administered solely for the purposes of treating, right?

MS. PIPER: Objection to form. And

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outside the scope of Dr. Trout's opinion.

A. I mean, again, pharmaceutically acceptable composition, as I've discussed in my report, would have to meet the criteria that I've discussed.

Q. Okay. Well, let's see here. On page -- on paragraph 63 of your report, you say, "Beyond meeting the specifications for the API and excipients discussed above, a pharmaceutical composition as a whole must meet a variety of specifications," and then you are referencing U.S. Food and Drug Administration Q6A specifications, test procedures, and acceptance criteria for new drug substances and new drug products.

So do -- does a pharmaceutical composition have to meet the specifications for -- that FDA sets forth for a new drug product?

A. First of all, just to -- it continues, what you read, to, colon, "Chemical Substances," the Q6A specifications for those. But, no, I'm not saying that it has to meet Q6A.

Q. Okay.

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A. I'm saying that's an example.

Q. Okay. So the specifications for the pharmaceutical composition, as you state it here, is going to be defined by the company producing the pharmaceutical composition and is going to take into account safety and efficacy, right?

A. Yes, that's what I've written.

Q. Okay. So if -- if the Boschelli group decided that the specifications for the composition in Boschelli met what they define to be acceptable for a pharmaceutical composition to administer to the animals, isn't it a pharmaceutical composition, according to your own opinion?

MS. PIPER: Objection to form.

A. No.

Q. You don't deny the compositions of Boschelli were given to the mice, right?

MS. PIPER: Objection to form.

A. They were administered to the mice.

Q. They were in administered --

A. They were administered to the mice.

Q. Administered -- right.

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Intraperitoneally, right?

A. Well, also orally.

Q. And they were in multiple times for the single mouse, right?

A. Yes. For -- I mean, the -- there's some details in the different experiments but, yes.

Q. Did they kill the mice by administering the drug?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. The mice were meant to be sacrificed, so they were eventually killed in these --

Q. Was the purpose of the drug -- to administer the drug for the purpose of killing the animal?

MS. PIPER: Objection. Outside the scope of Dr. Trout's opinion.

A. I think that the objective of the Boschelli study was not to kill the mice.

Q. What was the objective of the Boschelli folks in administering the composition containing bosutinib, TWEEN 80, and dextrose?

MS. PIPER: Objection. Outside the

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1 Trout - Confidential  
 2 scope of Dr. Trout's opinion and report.  
 3 A. I didn't speak in my report about the  
 4 specific objective, so I didn't express an  
 5 opinion about that.  
 6 Q. Okay. Right. So you don't know  
 7 whether they -- you don't have an opinion as to  
 8 whether or not they were administering the  
 9 composition for the purposes of assessing the  
 10 composition's potential to inhibit CML tumor  
 11 growth, right?  
 12 MS. PIPER: Objection. Outside the  
 13 scope of Dr. Trout's opinion and report.  
 14 A. Are you quoting from somewhere?  
 15 Because I --  
 16 Q. No. I was just asking a question.  
 17 A. Okay. Could you repeat the question,  
 18 please?  
 19 Q. You don't have an opinion as to  
 20 whether the Boschelli scientists were  
 21 administering the composition described in that  
 22 reference for the purposes of assessing the  
 23 composition's potential to inhibit tumor growth,  
 24 right?  
 25 MS. PIPER: Objection. Outside the

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1 Trout - Confidential  
 2 scope of Dr. Trout's opinion and report.  
 3 A. That's correct. I've not expressed an  
 4 opinion about that. I do not have an opinion on  
 5 that.  
 6 Q. Okay. Do you have an opinion as to  
 7 whether -- strike that.  
 8 And you also don't have an opinion as  
 9 to whether or not the composition was, in fact,  
 10 capable of inhibiting tumor growth in the mice,  
 11 right?  
 12 MS. PIPER: Objection. Outside the  
 13 scope of Dr. Trout's opinion and report.  
 14 A. That's right. I did not express an  
 15 opinion about that.  
 16 Q. Okay. Okay. If you could -- you have  
 17 your report in front of you there?  
 18 A. Yes.  
 19 Q. Okay. I'm just going to -- I have  
 20 some questions about some of the language in  
 21 your report.  
 22 Well, before I do that, could I take  
 23 you to Exhibit D in your binder, please.  
 24 A. Okay.  
 25 Q. I'm sorry. Exhibit DD.

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1 Trout - Confidential  
 2 A. Ah.  
 3 Q. Two Ds.  
 4 A. Okay. I'm there.  
 5 Q. Do you recognize this document?  
 6 A. Yes.  
 7 Q. And what is this document?  
 8 A. This is a -- FDA Guidance for Industry  
 9 INDs for Phase II and Phase III Studies:  
 10 Chemistry, Manufacturing, and Controls  
 11 Information.  
 12 Q. Okay. What are Phase II studies?  
 13 MS. PIPER: Objection. Outside the  
 14 scope of Dr. Trout's opinion and report.  
 15 A. And you mean just in general, or in  
 16 the context of --  
 17 Q. In the --  
 18 A. -- my report in the case?  
 19 Q. Sure. In the context of this  
 20 particular document, what is your understanding  
 21 of what a Phase II study would be?  
 22 A. So a Phase II study is part of the  
 23 clinical studies that -- that can be performed.  
 24 Q. In -- in humans, correct?  
 25 A. Yes. In -- with this -- with respect

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1 Trout - Confidential  
 2 to this document, it's for humans.  
 3 Q. Okay. And Phase III studies, what is  
 4 your understanding of what a Phase III study  
 5 would be, as that term is used in this document?  
 6 A. A Phase III study is another phase of  
 7 clinical studies used for pharmaceuticals.  
 8 Q. Okay. All right. And just for  
 9 clarity then, it is not your opinion that a  
 10 pharmaceutically acceptable composition has to  
 11 be a composition that satisfies the requirements  
 12 of FDA for use in Phase II studies, right?  
 13 MS. PIPER: Objection. Outside the  
 14 scope of Dr. Trout's opinion and report.  
 15 A. I didn't speak, I think, specifically  
 16 about that, but this is an example, on the other  
 17 hand, of -- of a composition that could meet the  
 18 criterion of pharmaceutically acceptable  
 19 composition.  
 20 Q. Okay. But it is possible that a  
 21 pharmaceutically acceptable composition could be  
 22 one that does not meet the requirements for use  
 23 in a Phase II study with humans, right?  
 24 MS. PIPER: Objection. Outside the  
 25 scope of Dr. Trout's opinion and report.

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A. I think my opinion was only about an example of what could -- in this context what could fall under pharmaceutical -- pharmaceutically acceptable excipient.

Q. Pharmaceutically acceptable excipient --

A. Pharmaceutically acceptable composition. Thank you.

Q. So your opinion was, it was limited -- so if I understand you correctly, your opinion was essentially to establish a pharmaceutical composition that you have confidence would meet the standard of pharmaceutically acceptable as that term is used in the patent?

MS. PIPER: Objection to form.

A. No, I wouldn't say it exactly that way. No.

Q. Okay. How did I get that wrong?

A. So my opinions in this report discuss the kind of issues that the person of ordinary skill in the art would -- would think about and engage in in analyzing whether a particular reference, Boschelli 2001 specifically, discloses pharmaceutically acceptable

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compositions or not. So that was really what my report was about.

Q. And your opinion about that is that, A, you don't know whether the -- the API used in that composition was sufficiently pure to meet the standard of pharmaceutically acceptable, right?

MS. PIPER: Objection to form.

A. I don't know if I would summarize it so cursorily. I have many pages on this. I mean, for example, in paragraph 69 it says, "As explained in more detail below," but it's kind of a summary statement on one aspect, "the chemical synthesis disclosed in Boschelli 2001 was not designed to lead to and likely not would have led to a pharmaceutically acceptable API."

So I don't know if I would summarize it just in a sentence as you did.

Q. Okay. So -- well, that was one of the things that I wanted to ask you about.

So you say it would not -- would -- likely would not have led to a pharmaceutically acceptable API. So you don't -- you don't foreclose the possibility that it was, in fact,

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a pharmaceutically acceptable API that was used in the composition of Boschelli, correct?

MS. PIPER: Objection to form.

A. It's -- you know, it's possible. What I say -- that's why I wrote here, it -- it was not designed to and likely would not have led to a pharmaceutically acceptable API. In other words, I didn't say it's absolutely certainly did not -- likely would not have led to and was not designed to lead to.

Q. So what gave you the opinion that it was not designed to lead to a pharmaceutically acceptable API?

A. Well, I expressed that in multiple pages, from my experience in pharmaceutical manufacturing research and with pharmaceutical manufacturing, and from the references that -- that I've included here in multiple paragraphs in this report, what's disclosed in Boschelli 2001 do not -- were not designed and -- to lead to and likely would have not led to a pharmaceutically acceptable API. So those are the categories of bases for that opinion.

Q. Yeah, it's interesting, I mean, you

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don't -- well, I guess you don't have an opinion as to what their intention was with respect to this composition. But certainly they say in the Boschelli reference that their purpose was to administer the composition to animals to gauge the potential of the API to inhibit tumor growth, right? That's what they say?

MS. PIPER: Objection to form.

Objection that this is outside the scope of Dr. Trout's opinion and report.

A. As you said, I don't have an opinion on that particular subject.

Q. Okay. So one thing you do -- an opinion you give regarding the API is that when creating a pharmaceutically acceptable active appropriate particle size and type, pressure, column length, and flow rate must all be taken into account.

Right? You say that at paragraph 71?

MS. PIPER: Objection to form.

A. Right. I think that you substantially read what I say at the bottom of page 22 in the middle of paragraph 71, and it has to be understood in the context of the paragraph in

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the section, too, but that's I think  
substantially what's written there.

Q. So is it your opinion a  
pharmaceutically acceptable active is one  
wherein the particle size of the active is  
known?

A. I don't have an opinion about that. I  
wanted to emphasize this appropriate -- I  
think -- this appropriate particle size we're  
talking about within the context of column  
chromatography, I'm talking about the particles  
in the chromatographic equipment.

Q. Okay. What, if anything, do you know  
about the particle size and type in the column  
chromatography apparatus used in Boschelli?

A. Well, Boschelli, for example, on  
page 3974, on the right column, the last full  
example, which references 31a, and I think I  
quote it in my report, too, but it says, "The  
residue is purified by column chromatography,"  
and the sentence continues.

And so Boschelli doesn't disclose  
that, and these are the kind of things that one  
would expect to be disclosed if one were to make

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a pharmaceutically acceptable composition.

Q. But what they say is that the residue  
is purified by column chromatography, right?

MS. PIPER: Objection to form.

Q. I mean, isn't that what they say,  
purified?

MS. PIPER: Objection to form.

A. I mean, that's what's written there,  
and I discuss this in my report.

Q. You don't believe them?

MS. PIPER: Object to form. And  
outside the scope of Dr. Trout's opinion.

A. I'm -- I don't -- I -- I see what's  
written there, and I -- I certainly believe  
them. I think the important thing is to  
understand the context of this purification.  
And I -- you know, I discuss this in multiple  
paragraphs, and I -- around paragraph 71 that we  
discussed, and before that in paragraph 70,  
and -- and beyond.

But I think it's important, in  
answering your question, in paragraph 70, I  
start out, "A POSA reading Boschelli 2001 would  
conclude that Compound 31a was synthesized

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without much attention paid to purification or  
to any of the specifications required for active  
compounds that are to be included in a  
pharmaceutical composition," and I go on.

So they purified it for a certain  
purpose, but not for the purpose of creating a  
pharmaceutical composition based on their  
disclosure.

Q. Okay. They don't say that, right?  
They don't say, we purified it -- strike that.

Boschelli doesn't say they made a  
crude purification of bosutinib, right?

A. Correct. So I mean, citing that,  
those are not the words that they use.

Q. Okay. Now, let me ask you a different  
question. Let's say for the sake of argument  
that it wasn't purified to the standards that  
would be required for a pharmaceutically  
acceptable active. At the time of the invention  
here, would a person of ordinary skill in the  
art have been able to synthesize bosutinib and  
purify it to a standard that would be -- would  
render it acceptable for use in a  
pharmaceutically acceptable composition?

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MS. PIPER: Objection. Outside the  
scope of Dr. Trout's opinion and report.

A. I haven't done that analysis, and I  
don't have an opinion on that.

Q. Okay. Let's say for the sake of  
argument the TWEEN 80 used in the composition of  
Boschelli was not pharmaceutical grade TWEEN 80,  
at the time of the invention would a person of  
ordinary skill in the art have been able to  
formulate a composition that included  
pharmaceutical grade TWEEN 80?

MS. PIPER: Objection. Outside of the  
scope of Dr. Trout's opinion and report.

A. I didn't express an opinion on that  
issue.

Q. Okay. Then let me ask you this  
question. At the time of the invention, could a  
person of ordinary skill in the art have  
reproduced the composition of Boschelli in such  
a way that it would meet the standard of a  
pharmaceutically acceptable compound or  
composition as you understand that claim to  
require?

MS. PIPER: Objection. Outside the

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1 Trout - Confidential  
 2 scope of Dr. Trout's opinion and report.  
 3 A. I don't have an opinion on that.  
 4 Q. Okay. What are the pH requirements  
 5 for a suspension being administered ip?  
 6 MS. PIPER: Objection. Outside the  
 7 scope of Dr. Trout's opinion and report.  
 8 A. I didn't express a -- such opinions.  
 9 I don't have an opinion on that.  
 10 Q. Are you aware of any pharmaceutically  
 11 acceptable compositions with a pH of  
 12 approximately 5.9 that have been administered to  
 13 animals ip?  
 14 MS. PIPER: Objection. Outside the  
 15 scope of Dr. Trout's opinion and report.  
 16 A. To the extent that you're not talking  
 17 about my paragraph 77, I don't have an opinion  
 18 on it. I mean, the pH 5.9 is in my paragraph  
 19 77.  
 20 Q. So this is something -- again, in --  
 21 sticking to paragraph 77, you say, "Were the  
 22 Boschelli composition intended to be a  
 23 pharmaceutical composition, potential issues  
 24 such as choosing a desired pH and maintaining it  
 25 would have likely been addressed."

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1 Trout - Confidential  
 2 A. I don't think I talk about adjustment  
 3 of pH. But I'm -- maybe if you could -- we're  
 4 still talking about paragraph 77?  
 5 Q. Uh-huh.  
 6 A. Again, my opinion is, potential issues  
 7 such as choosing a desired pH and maintaining it  
 8 would have likely been addressed, even reporting  
 9 it potentially. So that's what my opinion is  
 10 about.  
 11 Q. Okay. At the time of the invention  
 12 would persons of ordinary skill in the art know  
 13 how to choose and maintain the pH level for a  
 14 pharmaceutical composition?  
 15 A. I mean, I -- I think it depends on the  
 16 details. My point here -- in general, it might  
 17 or might not. My point here is that it -- it  
 18 doesn't even seem to be in the minds of the  
 19 authors of the paper, and it's something that  
 20 would have been -- would have come to mind  
 21 potentially or likely have been addressed.  
 22 Q. What is tonicity?  
 23 A. And I think you're referring, just to  
 24 clarify, to my paragraph 79?  
 25 Q. Just generally. But, yes, you do use

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 2 MS. PIPER: Objection to form.  
 3 Q. And my question to you is, it likely  
 4 would have been addressed but is it your opinion  
 5 that it's not necessary in all circumstances for  
 6 such things to be addressed?  
 7 A. Right. That's why I say "likely."  
 8 I'm not saying it's absolutely necessary. I say  
 9 that it's likely. And, again, this is one part  
 10 of the totality of the evidence which led me to  
 11 my conclusion.  
 12 Q. Okay. So is it possible that it  
 13 wasn't necessary for pH adjustment to be  
 14 addressed in the composition of Boschelli?  
 15 MS. PIPER: Objection. Outside the  
 16 scope of Dr. Trout's opinion.  
 17 A. Frankly, I don't understand the  
 18 question. But to the extent that I do, I think  
 19 it's outside of my scope of my opinions.  
 20 Q. To make sure that I understand, let me  
 21 rephrase the question. Can you envision a  
 22 scenario wherein it would not have been  
 23 necessary for the investigators in Boschelli to  
 24 adjust the pH of the composition they use to  
 25 administer to the mice?

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 2 that term in paragraph 79.  
 3 A. Okay. So just -- not -- I'm sorry.  
 4 I'm confused.  
 5 Q. I'm just asking, what is your  
 6 understanding of the term "tonicity"? What does  
 7 that mean?  
 8 A. Outside of the scope of my report but  
 9 just generally?  
 10 Q. I mean, specifically as you use it in  
 11 your report. You use the term, so I just want  
 12 to understand what it means to you.  
 13 A. Okay. What it means is a -- a  
 14 particular, let's say, concentration of -- of,  
 15 let's say, a -- an aqueous solution, the  
 16 different concentration of the solutes in that  
 17 solution leading to a value tonicity usually  
 18 measured in particular units like milliosmoles,  
 19 which is a measure of how -- how much solutes,  
 20 I'll say it that way, are in the solution,  
 21 concentration of such.  
 22 MR. BENSON: Okay. Why don't we  
 23 take -- I think I'm almost finished. Why  
 24 don't we take a short break, and I'll just  
 25 confer with my colleagues here. And we'll

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 2 come back and finish up. Okay?  
 3 THE WITNESS: Okay.  
 4 THE VIDEOGRAPHER: The time is  
 5 1:58 p.m., and we are going off the record.  
 6 (Recess from 1:58 to 2:14.)  
 7 THE VIDEOGRAPHER: The time is  
 8 2:14 p.m., and we are back on the record.  
 9 Q. Okay. Just a few more questions.  
 10 The patent in -- at issue here, the  
 11 '625 patent, also describes xenograftic studies  
 12 using bosutinib with mice, correct?  
 13 I'll direct you to, for example,  
 14 Column 13.  
 15 A. Yes. I see that, Column 13 and 14,  
 16 yes.  
 17 Q. Okay. So it says that the -- "The  
 18 compounds of formula 1 ('the compounds'),  
 19 originally identified as a Src inhibitor, are  
 20 shown here to be a potent anti-proliferative and  
 21 proapoptotic agent against CML cells in  
 22 culture."  
 23 Right? Did I read that correctly?  
 24 A. Yes, that's what's written there.  
 25 Yes.

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 2 A. I think it means oral administration.  
 3 Q. Thank you.  
 4 Now, let's go over to Column 14. It  
 5 says here -- now, this is describing the nude  
 6 mice data with the CML cell xenografts, correct?  
 7 Beginning at about, looks like line 3?  
 8 MS. PIPER: Objection. Outside of the  
 9 scope of Dr. Trout's opinion and report.  
 10 A. Yeah, I don't have an opinion on what  
 11 kind of cells those were.  
 12 Q. Okay. All right. Well, that's fine.  
 13 It says here that -- the very last  
 14 sentence says, "The compound of Example 1 was  
 15 administered p.o. in 0.4 percent  
 16 methocel/0.5 percent TWEEN at 75 mg/kilogram  
 17 once a day for 5 days (8 mice/group)."  
 18 Did I read that correctly?  
 19 A. Yes.  
 20 Q. Do you know what methocel is?  
 21 A. Yes.  
 22 Q. What is it?  
 23 A. It's a -- an abbreviation for  
 24 methylcellulose.  
 25 Q. Okay.

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 2 Q. And then next it says, "The apoptotic  
 3 activity of the compounds against CML cells in  
 4 culture is mirrored by its activity in vivo  
 5 against CML xenografts."  
 6 Right?  
 7 A. Yes, that's what's written.  
 8 Q. And it says, "The K562 tumors regress  
 9 in nude mice when the compounds are administered  
 10 p.o. once a day."  
 11 Right?  
 12 A. Yeah, I mean, just -- since you're  
 13 quoting didn't say "the" but, yeah,  
 14 substantially that's right.  
 15 Q. What does p.o. stand for? Do you  
 16 know?  
 17 MS. PIPER: Objection. Outside the  
 18 scope of Dr. Trout's opinion.  
 19 A. I -- I guess it's outside of my  
 20 opinion.  
 21 Q. Okay. I didn't really ask your  
 22 opinion. I just asked if you knew. You can  
 23 answer.  
 24 A. Yes, I know.  
 25 Q. Okay. What does it mean?

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 2 A. Or maybe not an abbrev -- a shortened  
 3 version of methylcellulose.  
 4 Q. And would this -- the .4 percent  
 5 methocel/.5 percent TWEEN, is this a -- is there  
 6 also water in this composition, as far as you  
 7 can understand?  
 8 MS. PIPER: Objection. Outside the  
 9 scope of Dr. Trout's opinion and report.  
 10 A. I didn't analyze it as such.  
 11 Q. Would you expect, based on the  
 12 description here, that there's also water in  
 13 this composition?  
 14 MS. PIPER: Objection. Outside the  
 15 scope of Dr. Trout's opinion and report.  
 16 A. I didn't offer an opinion about what  
 17 else is in the -- in this compound of Example 1,  
 18 and -- and the other things.  
 19 Q. Well, let me ask you this. This  
 20 composition that's described here in Column 14,  
 21 is that a pharmaceutically acceptable  
 22 composition?  
 23 MS. PIPER: Objection. Outside the  
 24 scope of Dr. Trout's opinion.  
 25 A. I don't have an opinion about whether



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that's pharmaceutically acceptable or not.  
Q. What would you need to know to make that determination?

A. Well, I would need to do a similar kind of analysis as to what's in my report, the analysis that I did for the Boschelli 2001.

MR. BENSON: Okay. I don't think I have any further questions for you, Dr. Trout. Thank you very much for your time.

THE WITNESS: You're welcome.

THE VIDEOGRAPHER: Is that it?

MR. BENSON: Before we go off the record, do we -- let's designate -- we'll designate this as confidential. I don't think there's anything but we'll just go through it and double-check, but for the time being we'll just designate it as confidential.

(Continued on following page to include jurat.)

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THE VIDEOGRAPHER: The time is 2:20 p.m., and this ends the deposition of Bernhardt Trout.  
(Time noted: 2:20 p.m.)

-----  
BERNHARDT TROUT, Ph.D.

Subscribed and sworn to before me this day of 2019.

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# C E R T I F I C A T E

STATE OF NEW YORK )  
) Ss.:

COUNTY OF NEW YORK )

I JEFFREY BENZ, a Certified Realtime Reporter, Registered Merit Reporter and Notary Public within and for the State of New York, do hereby certify:

That BERNHARDT TROUT, Ph.D., the witness whose examination is hereinbefore set forth, was duly sworn by me and that this transcript of such examination is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage; and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 14th of August, 2019.

-----  
JEFFREY BENZ, CRR, RMR

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Exhibit 3 Guide for the Care and Use 93 24  
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## ERRATA SHEET FOR THE TRANSCRIPT OF:

Case Name: Wyeth LLC v. Alembic Pharmaceuticals

Dep. Date: August 7, 2019

Deponent: Bernhardt Trout, Ph.D.

Pg. Ln.	Now Reads	Should Read	Reason
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\_\_\_\_\_  
Signature of Deponent

SUBSCRIBED AND SWORN BEFORE ME

THIS \_\_\_\_ DAY OF \_\_\_\_\_, 2019.

\_\_\_\_\_  
(Notary Public) MY COMMISSION EXPIRES: \_\_\_\_\_

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# **Exhibit C**

# Frequently Asked Questions About the Public Health Service Policy on Humane Care and Use of Laboratory Animals

Axel Wolff, MS, DVM, Nelson Garnett, DVM, Stephen Potkay, VMD, Carol Wigglesworth, Denis Doyle, MA, and Venita Thornton, DVM, MPH

**The authors answer eight questions commonly asked of the Office of Laboratory Animal Welfare concerning the Public Health Service Policy on Humane Care and Use of Laboratory Animals.**

The Office of Laboratory Animal Welfare (OLAW) of the National Institutes of Health (NIH) develops, implements, and oversees compliance with the US Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals*<sup>1</sup> (*Policy*). The PHS *Policy* and the US Department of Agriculture's (USDA's) Animal Welfare Regulations<sup>2</sup> are the two principal federal documents that set forth requirements for animal care and use by institutions using animals in research, testing, and education. One of OLAW's primary functions is to assist institutions in implementing PHS *Policy* by responding to policy-related questions. This is accomplished by collaborating with organizations and individuals in preparing guidance for Institutional Animal Care and Use Committees (IACUCs)<sup>3-5</sup>, supporting the publication of monographs on various aspects of animal care and use programs<sup>6,7</sup>, and publishing *Policy* interpretations in articles<sup>8-18</sup> and other formats<sup>19-30</sup>. OLAW also sponsors seminars and training that specifically address current topics covering animal care and use, and issues guidance notices in the NIH Guide for Grants and Contracts (formerly as "Dear Colleague" letters), all of which are found on the OLAW website (<http://grants.nih.gov/grants/olaw/olaw.htm>). The following represent several additional questions frequently asked by institutions and the OLAW responses.

**1. Does the IACUC need to require that the investigator submit the grant application, or portions thereof, along with the IACUC animal use protocol form for review by the IACUC? Is the IACUC**

**required to compare the two for consistency?**

PHS *Policy* (IV.D.) requires the institution to verify, before award, that the IACUC has reviewed and approved those components of grant applications and contract proposals related to the care and use of animals. This position is reiterated in NIH Grants Policy Statement under Part II, Terms and Conditions. Most institutions have developed an IACUC protocol form and require investigators to provide detailed information about the proposed use of the animals on this form. The signature of the authorized institutional official on any PHS application or proposal indicates the organization's commitment to comply with the laws, regulations, and policies to which an activity is subject. Institutional submission of IACUC approval, subsequent to submission of the application/proposal, must represent approval of the information originally submitted in the application/proposal, or include notification of any significant changes required by the IACUC.

Although there is no explicit requirement for the IACUC to do a side-by-side comparison of the application/proposal and the IACUC protocol review form, it is an institutional responsibility to ensure that the information the IACUC reviews and approves is consistent with that contained in the application/proposal to be funded. Institutions are free to devise a workable mechanism to accomplish this end. One excellent way to prevent problems of inconsistencies between the information submitted to the PHS and that on the IACUC protocol review form is to implement a procedure for direct compar-

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ison<sup>23</sup>. If a procedure of direct comparison is adopted, the individual(s) charged with conducting the comparison should be appropriately qualified to identify inconsistencies. Some institutions have delegated this responsibility to a particular office or position (e.g., sponsored programs office, compliance office); others have asked Departmental Chairs to verify consistency<sup>31</sup>.

2. Our IACUC has several categories for the approval of animal study protocols. Which one to use depends on the kinds of issues it identifies during review. We are sometimes unsure how best to characterize the approval status of these projects. Can OLAW provide any advice as to what constitutes appropriate terminology for approval of a protocol?

The PHS *Policy* recognizes only three outcomes of IACUC reviews of proposed activities (protocols) related to animal care and use, as well as proposals for significant changes in previously approved ongoing activities. They are 'approve', 'withhold approval', and 'require modifications to secure approval'. OLAW is aware that some institutions have chosen to use different words and phrases to characterize the latter of these outcomes, such as 'conditionally approved', 'approval pending', 'provisionally approved', 'approved with stipulations', 'administrative approval', and 'limited approval'. We should note that several incidents of suspensions and noncompliance are reported by institutions to OLAW each year that are related to the conduct of unauthorized animal studies by investigators who have misinterpreted IACUC responses or the approval categorization of their proposals. To avoid such misunderstandings and the subsequent necessities to take corrective actions and report to OLAW, this Office recommends that IACUCs use language that is as unambiguous as possible in communicating the results of their reviews of animal study protocols. We suggest that institutions can do this by adhering to the language of the *Policy* and avoiding use of the words 'approved' and 'approval' to describe the

outcome of any review that is not an unequivocal approval and making it known that no animal work may commence without an unequivocal approval. In addition, the IACUC approval date submitted to PHS agencies as part of a grant application or contract proposal must reflect the date of final approval.

3. Are the scientists at our institution allowed to use non-pharmaceutical-grade chemical compounds in physiological preparations involving laboratory animals? Please clarify whether this is an allowable practice and whether it makes a difference if the compounds are used in survival versus nonsurvival experiments.

The use of non-pharmaceutical-grade chemical compounds in experimental animals under certain circumstances has been, and will continue to be, a necessary and acceptable component of biomedical research. OLAW and the USDA have determined that their use should be based on (1) scientific necessity, (2) nonavailability of an acceptable veterinary or human pharmaceutical-grade compound, and (3) specific review and approval by the IACUC<sup>32</sup>. In preparing and reviewing proposals to use non-pharmaceutical-grade products, investigators and IACUCs should consider a number of related animal welfare and scientific issues including safety, efficacy, and the inadvertent introduction of research-complicating variables. Although one can assume that issues such as sterility, pyrogenicity, stability, pharmacokinetics, and quality control have been addressed during the course of producing pharmaceutical-grade drugs, one cannot say the same for substances produced in the research laboratory using non-pharmaceutical-grade chemical compounds. Cost savings alone do not adequately justify the use of non-pharmaceutical-grade compounds in animals. Although the potential animal welfare consequences of complications are less evident in nonsurvival studies, the scientific issues remain the same. The principles and need for professional judgment just outlined still apply.

4. Because of time constraints and the needs of our investigators, our IACUC reviews some protocols by sending each member a copy and then polling them to determine whether they approve. Is this procedure in compliance with the PHS *Policy* if the IACUC members, at a subsequent full-Committee meeting, are asked to reaffirm their votes? Is this procedure appropriate, and if not, what must we do to correct the situation?

No. The initial polling of members is not sufficient for approval and initiation of work on animals. Only full Committees or designated members can approve animal study protocols, in accordance with the PHS *Policy* (IV.C.2). IACUC members may use electronic or other forms of polling to call for a full-Committee review, but not to vote<sup>12,17</sup>. Any animal studies undertaken on the basis of approvals resulting from such polling would not be compliant with the PHS *Policy*. Recognizing that urgency may sometimes be an issue in considering animal study protocols, the PHS *Policy* allows for designated review by at least one qualified member, appointed by the IACUC Chair, provided that all other voting members have had an opportunity to request full review and that no member requests a full-Committee review.

5. Several investigators at our institution wish to use surgically modified animals in their research but do not want to perform the surgery in-house. We are considering the purchase of such animals and would like to know whether the PHS *Policy* applies to customized surgery performed at vendor facilities.

The PHS *Policy* is applicable to all PHS-supported activities involving animals, whether the activities are performed at a PHS agency, an awardee institution, or other institution (PHS *Policy* at I., II., III., and V.B.). OLAW has provided guidance regarding animal use (antibody production) that takes place outside the applicant/assured institution through subgranting or subcontracting<sup>33</sup>. That guidance may also serve as a template for determining whether other activities such as

customized surgery are covered by the PHS *Policy*. In this regard, and with respect to applicability of the PHS *Policy*, a determining issue is whether the surgery is conducted in response to a specific custom request or whether the animals were previously modified and available before the request was made. If an investigator requests that a specific custom surgical procedure or procedures be performed on an animal for use in activities funded by the PHS, then the organization that conducts the procedure(s) is considered a performance site and must either have on file with OLAW an approved Animal Welfare Assurance or be included as a component of the applicant organization's Assurance.

6. We are a small antibody producer using rabbits, mice, and goats, and our work supports numerous clients, including some funded by the PHS. When we applied for an Assurance, OLAW informed us that we could not approve one 'blanket protocol' to cover all of our antibody production procedures, even though the work is essentially always the same. Please clarify.

Provisions of the PHS *Policy* apply to all Assured institutions regardless of their size or mission. They include the requirement for the IACUC to "review and approve, require modifications in (to secure approval) or withhold approval of those components of PHS-conducted or supported activities related to the care and use of animals," (PHS *Policy* at IV.B.6.) on a project-specific basis. Consequently, each proposed protocol involving antibody production as well as significant changes (e.g., amendments) to previously approved protocols must be submitted for IACUC review and approval, taking into account the aims of the study and the methods proposed to avoid or minimize pain or distress to the animals (PHS *Policy* at IV.C.1.). For example, reviews of proposed ascites monoclonal antibody production in mice must also critically address alternative (*in vitro*) methods as well as pain and distress issues<sup>6,33</sup>. Another example would be a request for a custom antibody against a

specific protein for the purpose of vaccine development, followed by a request for an antibody against a different protein to be used for the same purpose. In both instances, *Policy* would require either an amendment or a new protocol. As is the case with any new protocol or proposed significant change to a previously approved protocol, the PHS *Policy* allows for either full-Committee or designated-member review. OLAW recognizes that many aspects of antibody production are routine and recommends that institutional Standard Operating Procedures (SOPs) be developed that describe species-specific techniques for immunization, titer determinations, volume blood collection, and associated procedures. One may cite IACUC-approved SOPs in proposed project-specific protocols or proposed amendments to avoid needless repetition. Under these circumstances, it is possible to combine multiple projects, or even multiple investigators, under a single protocol. However, for PHS *Policy* purposes, IACUC approval of each project-specific protocol submission or amendment must be readily identifiable and amenable to tracking.

7. May a former employee or former student of our institution be considered for appointment to our IACUC as a nonaffiliated member?

PHS *Policy* (IV.A.3.b.4.) defines the nonaffiliated member as an "individual who is not affiliated with the institution in any way other than as a member of the IACUC, and is not a member of the immediate family of a person who is affiliated with the institution," and the USDA's Animal Welfare Regulations expect the individual to "provide representation for the general community interest<sup>34</sup>." The *Guide*<sup>3</sup>, which calls this person the "public member," requires additionally that the individual not be a current laboratory animal user. Regarding the service of a former employee in the capacity of a nonaffiliated member, the appointing official would have to receive assurance that the person is not in any way conflicted or beholden to the institution<sup>35</sup>. If there are no discernable

ties or ongoing affiliation with the institution, then it would be permissible to consider appointment of the former employee or former student to the IACUC. It is important for officials who appoint IACUC members to determine whether real or perceived conflicts of interest exist and make the appropriate choices to avoid criticism about the institution's or the Committee's integrity. Choosing an individual who is unambiguously 'nonaffiliated' is the best way to fulfill the letter and the spirit of this provision.

8. Our IACUC has encountered a problem with investigators who do not submit their protocols for review in time to gain approval before the three-year expiration date. Is it permissible to grant an administrative extension of IACUC approval so as to avoid expiration?

No. For PHS purposes, IACUC review following the provisions at IV.C.2. of the PHS *Policy* must be accomplished at least once every three years<sup>1</sup>. The IACUC may not extend the three-year approval by any means other than IACUC review and approval using the procedures of IV.C.2. When IACUC approval expires, it is no longer valid. Continuation of animal activities beyond the expiration is a serious and reportable violation of PHS *Policy*.

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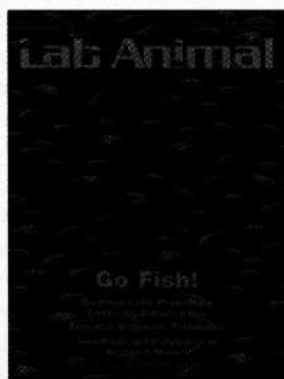
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